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PYRAZOLOPYRIDINE DERIVATIVES

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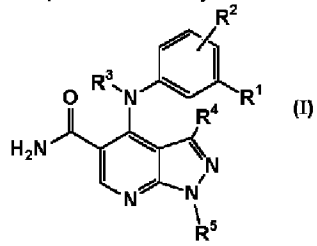
SPECIFICATION

(57) Abstract

Construction

Pyrazolopyridine derivatives represented by formula (I) and non-toxic salts thereof



(I)

(wherein, R^1 denotes an alkyl, alkylthio, alkyl substituted by hydroxy group or the like, and the like, R^2 denotes a hydrogen atom or alkoxy group, R^3 denotes a hydrogen atom or

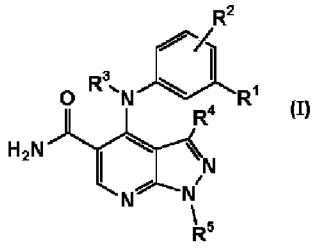
alkyl, R^4 denotes a hydrogen atom, alkyl, cycloalkyl, cycloalkyl-substituted alkyl, halo-substituted phenyl, or mono-, bi- or tricyclic heteroring containing N, O and/or S, and R^5 denotes a hydrogen atom, alkyl, cycloalkyl, cycloalkyl substituted alkyl group or (substituted) phenyl).

Effect

The compounds of formula (I) have PDE4 inhibiting activity and are useful in the prevention and/or treatment of inflammatory diseases, diabetic diseases, allergic diseases, autoimmune diseases, osteoporosis, obesity, anti-depression (sic), Parkinson's disease, ischemic reperfusion disorder, leukaemia and the like.

Patent Claim

1. Pyrazolopyridine derivatives represented by general formula (I) and non-toxic salts thereof.



(I)

(wherein, R^1 denotes 1) a group $-OR^6$, 2) a group $-SR^7$, 3) a C2-8 alkynyl group, 4) a nitro group, 5) a cyano group, 6) a C1-8 alkyl group substituted by a hydroxy group or a C1-8 alkoxy group, 7) a phenyl group, 8) a group $-C(O)R^8$, 9) a group $-SO_2NR^9R^{10}$, 10) a group $-NR^{11}SO_2R^{12}$, 11) a group $-NR^{13}C(O)R^{14}$ or 12) a group $-CH=NR^{15}$,

R^6 and R^7 denote i) a hydrogen atom, ii) a C1-8 alkyl group, iii) a C1-8 alkyl group substituted by a C1-8 alkoxy group, iv) a trihalomethyl group, v) a C3-7 cycloalkyl group, vi) a C1-8 alkyl group substituted by a phenyl group or vii) a 3-15 membered mono-, di- or tricyclic hetero ring containing 1-4 nitrogen atoms, 1-3 oxygen atoms and/or 1-3 sulphur atoms,

R^8 denotes a C1-8 alkyl group, a phenyl group, a group $-NR^{16}R^{17}$ or a group $-NR^{18}NR^{19}R^{20}$; R^9 and R^{10}, and also R^{11} and R^{13}, each independently denote a hydrogen atom or a C1-8 alkyl group, R^{12} denotes a C1-8 alkyl group, R^{14} denotes a C1-8 alkyl group, a C1-8 alkoxy group or a group $-NR^{21}R^{22}$, R^{15} denotes a hydroxy group, a C1-8 alkoxy group or $-NR^{23}R^{24}$, R^{16} and R^{17}; R^{18}, R^{19} and R^{20}; R^{21} and R^{22}; and also R^{23} and R^{24} each

independently denote a hydrogen atom or a C1-8 alkyl group,

R^2 denotes 1) a hydrogen atom or 2) a C1-8 alkoxy group,

R^3 denotes 1) a hydrogen atom or 2) a C1-8 alkyl group,

R^4 denotes 1) a hydrogen atom, 2) a C1-8 alkyl group, 3) a C3-7 cycloalkyl group, 4) a C1-8 alkyl group substituted by a C3-7 cycloalkyl group, 5) a phenyl group which may be substituted by 1-3 halogen atoms or 6) a 3-15 membered mono-, di- or tricyclic hetero ring containing 1-4 nitrogen atoms, 1-3 oxygen atoms and/or 1-3 sulphur atoms, and

R^5 denotes 1) a hydrogen atom, 2) a C1-8 alkyl group, 3) a C3-7 cycloalkyl group, 4) a C1-8 alkyl group substituted by a C3-7 cycloalkyl group or 5) a phenyl group which may be substituted by 1-3 substituents selected from the following i) -iii);

i) a C1-8 alkyl group, ii) a C1-8 alkoxy group, iii) a halogen atom, and,

the 3-15 membered mono-, di- or tricyclic hetero ring containing 1-4 nitrogen atoms, 1-3 oxygen atoms and/or 1-3 sulphur atoms represented by R^4, R^6 and R^7 may be substituted by 1-3 substituents selected from the following i) -iii) (sic);

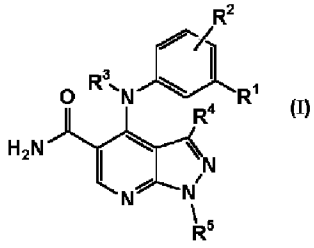
i) a C1-8 alkyl group, ii) a C1-8 alkoxy group, iii) a halogen atom, iv) a carboxy-group, v) a C1-8 alkoxycarbonyl group, vi) a C2-8 acyl group, vii) a group $-SO_2$-C1-8 alkyl, viii) an oxo group).

Detailed Description of the Invention

(0001)

Technical Sphere of this Invention

This invention relates to pyrazolopyridine derivatives. More particularly, this invention relates to (1) pyrazolopyridine derivatives represented by general formula (1) and non-toxic salts thereof,



(I)

(wherein, all the symbols have the same meanings as described hereinafter),

(2) a process for the production thereof and (3) a drug agent containing them as an effective ingredient.

(0002)

Background of the Invention

Cyclic adenosine-3',5'-mono phosphate (c-AMP) and cyclic guanosine-3',5'-mono phosphate (c-GMP) are signal transduction substances in cells (second messengers), and are decomposed to inert 5'-AMP and 5'-GMP respectively by a group of hydrolases called phosphodiesterase (PDE). The PDE isozymes that deactivate these substances are not uniformly present within the living body, but are present in-vivo with an organ specific localisation showing differences in cell distribution or tissue distribution. So far, the existence of 11 species of the family from PDE 1 to PDE 11 has been confirmed. (cf. Current opinion in Cell Biology, 12, 174-179 [2000]).

(0003)

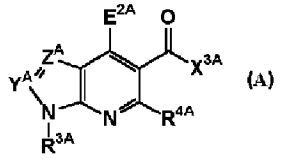
Among these PDEs, PDE4 is present in various kinds of cells including respiratory tract smooth muscle, epithelial cells, inflammatory cells (macrophages, neutrophils, eosinophils), T-lymphocytes and the like and this controls the intracellular c-AMP levels in these cells, and carries out regulation of cell function. On the other hand, PDE5 is present in platelets, myocardium or vascular smooth muscle and the like and controls intracellular c-GMP levels, and is involved in the regulation of the circulatory system. Therefore it is known that PDE4 inhibitors have a bronchodilating action, antiinflammatory action, mediator release inhibitory action or immunosuppression action because PDE4 inhibitors cause the accumulation of intracellular c-AMP due to inhibition of the decomposition of c-AMP by PDE4. Accordingly agents which specifically hinder PDE4 are thought to be useful in the prevention and/or treatment of various diseases, namely inflammatory diseases (asthma, obstructive lung disease, septicaemia, nephritis, hepatitis and the like), diabetic diseases, allergic diseases (allergic rhinitis, allergic conjunctivitis, atopic dermatitis and the like), autoimmune diseases (ulcerative colitis, Crohn's disease, rheumatism, psoriasis, multiple sclerosis, collagen disease and the like), osteoporosis, obesity, anti-depression (sic), Parkinson's disease, ischemic reperfusion disorder, leukaemia (Exp., Opin. Invest. Drugs, 8, 1301-1325 [1999]) and the like without demonstrating the action on the circulatory organs caused by PDE 5.

(0004)

Technology of the Prior Art

As far as pyrazolopyridine derivatives are concerned, for example a compound

represented by general formula (A) and pharmacologically acceptable salts thereof are stated to have a c-GMP phosphodiesterase (PDE 5) inhibiting action in WO2000/15222.



(A)

(wherein, E^{2A} denotes an aryl substituted by -NH-A^{1A}- (in the group, A^{1A} denotes a C1-10 alkylene or substituted alkylene) or the like, X^{3A} denotes -N(R^{9A})(R^{10A}) (in the group, R^{9A} and R^{10A} denote a hydrogen atom, alkyl or the like), Y^A denotes a nitrogen atom or the like, Z^A denotes a nitrogen atom or C(R^{7A}) (in the group, R^{6A} (sic) denotes a hydrogen atom, alkyl or the like), R^{3A} denotes a hydrogen atom, alkyl, cycloalkyl or the like, and R^{4A} denotes a hydrogen atom and the like (the necessary parts have been extracted as far as the description of the groups is concerned).

(0005)

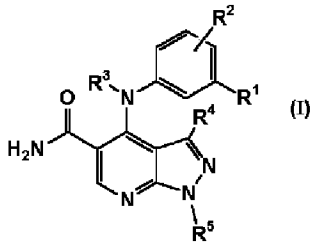
The Object of the Invention

These inventors carried out assiduous investigations to discover compounds having PDE4 inhibiting activity, and as a result discovered that this object was achieved with pyrazolopyridine derivatives represented by general formula (I). This invention was completed on the basis of this discovery.

(0006)

Disclosure of the Invention

This invention relates to (1) pyrazolopyridine derivatives represented by general formula (I) and non-toxic salts thereof



(I)

(0007)

(wherein, R^1 denotes 1) a group OR^6, 2) a group SR^7, 3) a C2-8 alkynyl group, 4) a nitro group, 5) a cyano group, 6) a C1-8 alkyl group substituted by hydroxy group or a C1-8

alkoxy group, 7) a phenyl group, 8) a group -C(O)R^8, 9) a group -$SO_2NR^9R^{10}$, 10) a group -$NR^{11}SO_2R^{12}$, 11) a group -$NR^{13}C(O)R^{14}$ or 12) a group -CH=NR^{15},

(0008)

R^6 and R^7 denotes i) a hydrogen atom, ii) a C1-8 alkyl group, iii) a C1-8 alkyl group substituted by a C1-8 alkoxy group, iv) a trihalomethyl group, v) a C3-7 cycloalkyl group, vi) a C1-8 alkyl group substituted by phenyl group or vii) a 3-15 membered mono-, di- or tricyclic heteroring containing 1-4 nitrogen atoms, 1-3 oxygen atoms and/or 1-3 sulphur atoms, R^8 denotes a C1-8 alkyl group, a phenyl group, a group -$NR^{16}R^{17}$ or a group -$NR^{18}NR^{19}R^{20}$, and R^9 and R^{10}, and also R^{11} and R^{13}; each independently denote a hydrogen atom or a C1-8 alkyl group, R^{12} denotes a C1-8 alkyl group, R^{14} denotes a C1-8 alkyl group, a C1-8 alkoxy group or a group -$NR^{21}R^{22}$, R^{15} denotes a hydroxy group, a C1-8 alkoxy group or -$NR^{23}R^{24}$, R^{16} and R^{17}; R^{18}, R^{19} and R^{20}; R^{21} and R^{22}; and also R^{23} and R^{24} each independently denote a hydrogen atom or a C1-8 alkyl group,

(0009)

R^2 denotes 1) a hydrogen atom or 2) a C1-8 alkoxy group and R^3 denotes 1) a hydrogen atom or 2) a C1-8 alkyl group,

(0010)

R^4 denotes 1) a hydrogen atom, 2) a C1-8 alkyl group, 3) a C3-7 cycloalkyl group, 4) a C1-8 alkyl group substituted by a C3-7 cycloalkyl group, 5) a phenyl group which may be substituted by 1-3 halogen atoms or 6) a 3-15 membered mono-, di- or tricyclic hetero ring containing 1-4 nitrogen atoms, 1-3 oxygen atoms and/or 1-3 sulphur atoms,

(0011)

R^5 denotes 1) a hydrogen atom, 2) a C1-8 alkyl group, 3) a C3-7 cycloalkyl group, 4) a C1-8 alkyl group substituted by a C3-7 cycloalkyl group, 5) a phenyl group optionally substituted by 1-3 substituents selected from the following i) -iii);

i) a C1-8 alkyl group, ii) a C1-8 alkoxy group and iii) a halogen atom,

(0012)

The 3-15 membered mono-, di- or tricyclic hetero ring including 1-4 nitrogen atoms, 1-3 oxygen atoms and/or 1-3 sulphur atoms represented by R^4, R^6 and R^7 may be optionally substituted by 1-3 substituents selected from the following i)-iii) (sic);

i) a C1-8 alkyl group, ii) a C1-8 alkoxy group, iii) a halogen atom, iv) a carboxy-group, v) a C1-8 alkoxycarbonyl group, vi) a C2-8 acyl group, vii) a group -SO_2-C1-8 alkyl and viii) an oxo group).

(0013)

This invention also relates to (2) a process for the production thereof and (3) a drug agent containing these as effective ingredients.

(0014)

In general formula (I), C1-8 alkyl groups comprise methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl and the isomers thereof. In general formula (I), C2-8 alkynyl groups comprise ethinyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl group and the isomers thereof. In general formula (I), C1-8 alkoxy groups comprise methoxy, ethoxy, propoxy, butoxy, pentyloxy, hexyloxy, heptyloxy, octyloxy group and the isomers thereof.

(0015)

In general formula (I), C1-8 alkoxycarbonyl groups comprise methoxycarbonyl, ethoxycarbonyl, propoxy carbonyl, butoxycarbonyl, pentyloxy carbonyl, hexyloxy carbonyl, heptyl oxycarbonyl, octyloxy carbonyl group and the isomers thereof. In general formula (I), C2-8 acyl groups comprise acetyl, propionyl, butyryl, valeryl, hexanoyl, heptanoyl, octanoyl group and the isomers thereof.

(0016)

In accordance with this invention, halogen atom denotes chlorine, bromine, fluorine, or iodine atom. In general formula (I), trihalomethyl groups comprise a methyl group tri-substituted by a chlorine, bromine, fluorine or iodine atom. In general formula (I), C3-7 cycloalkyl groups comprise cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl group and the isomers thereof.

(0017)

In general formula (I), 3-15 membered mono-, di- or tricyclic hetero rings containing 1-4 nitrogen atoms, 1-3 oxygen atoms and/or 1-3 sulphur atoms comprise 5-18 (sic) membered mono-, di- or tricyclic heteroaryl containing 1-4 nitrogen atoms, 1-3 oxygen atoms and/or 1-3 sulphur atoms or such heterorings wherein some or all of the rings are

saturated.

(0018)

Examples of 3-15 membered mono-, di- or tricycic heteroaryls containing 1-4 nitrogen atoms, 1-3 oxygen atoms and/or 1-3 sulphur atoms include for example pyrrole, imidazole, triazole, tetrazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, azepine, diazepine, furan, pyran, oxepine, thiophene, thiaine (thiopyran), thiepin, oxazole, isoxazole, thiazole, isothiazole, furazane, oxadiazole, oxazine, oxadiazine, oxazepine, oxadiazepine, thiadiazole, thiazine, thiadiazine, thiazepine, thiadiazepine, indole, isoindole, benzofuran, isobenzofuran, benzo thiophene, isobenzothiophene, indazole, quinoline, isoquinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, benzoxazole, benzothiazole, benzimidazole, benzoxepine, benzoxaazepine, benzoxadiazepine, benzothiepine, benzothiaazepine, benzothiadiazepine, benzoazepine, benzodiazepine, benzofurazan, benzothiadiazole, benzotriazole, carbazole, acridine, dibenzofuran, dibenzothiophene ring and the like.

(0019)

Examples of 3-15 mono-, bi- or tricyclic heterocycles containing 1-4 nitrogen atoms, 1-3 oxygen atoms and/or 1-3 sulphur atoms in which some or all the rings are saturated, include for example pyrroline, pyrrolidine, imidazoline, imidazolidine, pyrazoline, pyrazolidine, triazoline, triazolidine, tetrazoline, tetrazolidine, dihydropyridine, tetrahydropyridine, piperidine, dihydropyrazine, tetrahydropyrazine, piperazine, dihydropyrimidine, tetrahydropyrimidine, perhydropyrimidine, dihydropyridazine, tetrahydropyridazine, perhydropyridazine, dihydroazepine, tetrahydroazepine, perhydroazepine, dihydrodiazepine, tetrahydrodiazepine, perhydrodiazepine, dihydrofuran, tetrahydrofuran, dihydropyran, tetrahydropyran, dihydrothiophene, tetrahydrothiophene, dihydrothiaine (dihydrothiopyran), tetrahydrothiaine (tetrahydrothiopyran), dihydroxazole, tetrahydroxazole, dihydroisoxazole, tetrahydroisoxazole, dihydrothiazole, tetrahydrothiazole, dihydroisothiazole, tetrahydroisothiazole, dihydroxadiazole, tetrahydroxadiazole, dihydrothiodiazole, tetrahydrothiodiazole, tetrahydroxadiazine, tetrahydrothiadiazine, tetrahydroxazepine, tetrahydroxadiazepine, perhydroxazepine, perhydroxadiazepine, tetrahydrothiazepine, tetrahydrothiadiazepine, perhydrothiazepine, perhydrothiadiazepine, morpholine, thiomorpholine, indoline, isoindoline, dihydrobenzofuran, perhydrobenzofuran, dihydroisobenzofuran, perhydroisobenzofuran,

dihydrobenzothiophene, perhydrobenzothiophene, dihydroisobenzothiophene, perhydroisobenzothiophene, dihydroindazole, perhydroindazole, dihydroquinoline, tetrahydroquinoline, perhydroquinoline, dihydroisoquinoline, tetrahydroisoquinoline, perhydroisoquinoline, dihydrophthalazine, tetrahydrophthalazine, perhydrophthalazine, dihydronaphthyridine, tetrahydronaphthyridine, perhydronaphthyridine, dihydroquinoxaline, tetrahydroquinoxaline, perhydroquinoxaline, dihydroquinazoline, tetrahydroquinazoline, perhydroquinazoline, dihydrocinnoline, tetrahydrocinnoline, perhydrocinnoline, dihydrobenzoxazole, perhydrobenzoxazole, dihydrobenzothiazole, perhydrobenzothiazole, dihydrobenzoimidazole, perhydrobenzimidazole, dihydrocarbazole, tetrahydrocarbozole, perhydrocarbazole, dihydroacridine, tetrahydroacridine, perhydroacridine, dihydrodibenzofuran, dihydrodibenzothiophene, tetrahydrodibenzofuran, tetrahydrodibenzothiophene, perhydrodibenzofuran, perhydrodibenzothiophene, dioxolane, dioxane, dithiolane, dithiane, benzodioxalane, benzodioxane, benzodithiolane, benzodithiane ring and the like.

(0020)

In this invention, all isomers are included unless otherwise specifically indicated. For example, alkyl groups, alkoxy groups and alkylene groups include the straight chained and branched chain species. Moreover, isomers arising as a result of double bonds, rings, condensed rings (E, Z, cis, trans isomers), isomers due to the presence of asymmetric carbons (R, S isomers, α, β isomers, enantiomers, diastereomers), optically active isomers having optical rotation (D, L, d, l isomers), the polar bodies obtained by chromatographic separation (high polarity isomers, low polarity isomers), compounds in equilibrium, mixtures of arbitrary proportions thereof and racemic mixtures are all included in this invention.

(0021)

In this invention, as would be clear to a person skilled in the art, unless otherwise specifically indicated, the symbol

denotes that the bond is going away from the plane of the paper (in other words an α-configuration),

denotes that the bond is coming upwards from the plane of the paper (in other words an β-configuration), and

denotes α-, β- or a mixture thereof.

(0022)

The compound represented by general formula (I) may be converted into a non-toxic salt in accordance with a well known method. Examples of non-toxic salts include alkali metal salts, alkaline earth metal salts, ammonium salts, amine salts, acid addition salts, solvates and the like. Non-toxic water soluble salts are preferred. Examples of suitable salts include salts of alkali metals (sodium, potassium and the like), salts of alkaline earth metals (calcium, magnesium and the like), ammonium salts and salts of pharmacologically acceptable organic amines (tetramethylammonium, triethylamine, methylamine, dimethylamine, cyclopentylamine, benzylamine, phenethylamine, piperidine, monoethanolamine, diethanolamine, tris (hydroxymethyl) aminomethane, lysine, arginine, N-methyl-D-glucamine and the like).

(0023)

The acid addition salts are preferably non-toxic and water soluble. Suitable acid addition salts include for example inorganic acid salts such as nitrates, hydrochlorides, hydrobromides, hydroiodides, sulphates, phosphates, and organic acid salts such as acetates, lactates, tartrates, benzoates, citrates, methane sulphonates, ethane sulphonates, benzene suplhonates, toluene sulphonates, isethionates, glucuronates and gluconates.

(0024)

The solvates are preferably non-toxic and water soluble. Examples of suitable solvates include solvates of for example water and alcohol system solvents (for example ethanol and the like).

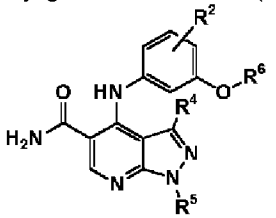
(0025)

Examples of R^1 in general formula (I) include the groups $-OR^6$ and $-SR^7$, and the group $-OR^6$ is preferred. Preferred examples of the R^6 group include C1-8 alkyl groups and 3-15 membered mono-, di- or tricyclic hetero rings containing 1-4 nitrogen atoms, 1-3 oxygen atoms and/or 1-3 sulphur atoms; a methyl group, ethyl group or pyrrolidine being particularly preferred. As R^2 in general formula (I), a hydrogen atom is preferred. As R^3 in general formula (I), a hydrogen atom is preferred. As R^4 in general formula (I), a C1-8 alkyl

group or cycloalkyl group is preferred, and in particular a methyl, ethyl, cyclopropyl, cyclobutyl or cyclopentyl group is preferred. As R^5 in general formula (I), a C1-8 alkyl group, C3-7 cycloalkyl group or phenyl group is preferred, and a methyl, ethyl, propyl or butyl group is particularly preferred.

(0026)

Among the compounds represented by general formula (I), preferred compounds comprise compounds represented by general formula (I-A).

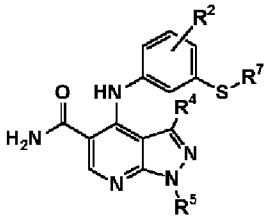


(I-A)

(wherein, all the symbols have the same aforesaid definitions) and

(0027)

compounds represented by general formula (I-B).



(I-B)

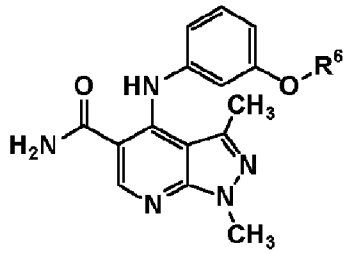
(wherein, all the symbols have the same aforesaid definitions).

(0028)

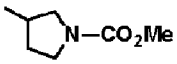
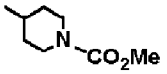
Examples of compounds of this invention include the compounds shown in Tables 1-10 and the compounds of the Examples and the non-toxic salts, acid addition salts and solvate salts thereof. Moreover, in each of the following Tables, Me denotes a methyl group, Et denotes an ethyl group, i-Pr denotes an isopropyl group and all other symbols have the same aforesaid definitions.

(0029)

Table 1



(I-A-1)

No.	R^6	No.	R^6
1	H	11	
2	Me	12	
3	Et	13	
4	i-Pr	14	
5		15	
6		16	
7		17	
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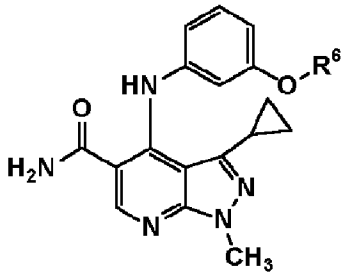
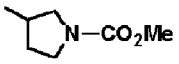
9		19	
10		20	

(0030)

Table 2



(I-A-2)

No.	R^6	No.	R^6
1	H	11	
2	Me	12	
3	Et	13	
4	i-Pr	14	
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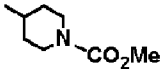
6		16	
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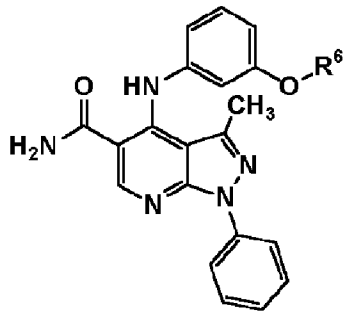
9		19	
10		20	

(0031)

Table 3



(I-A-3)

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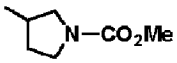
3	Et	13	
4	i-Pr	14	
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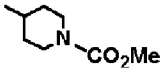
6		16	
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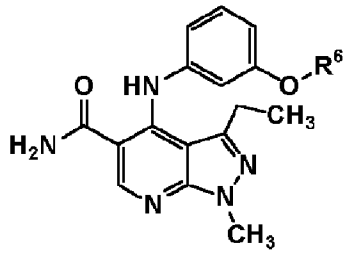
9		19	
10		20	

(0032)

Table 4



(I-A-4)

No.	R^6	No.	R^6
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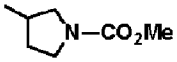
2	Me	12	
3	Et	13	
4	i-Pr	14	
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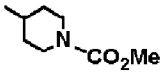
6		16	
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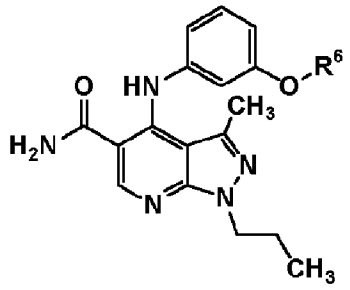
10		20	

J2002-020386
(unexamined)

(0033)

Table 5



(I-A-5)

No.	R^6	No.	R^6
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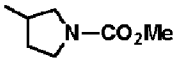
2	Me	12	
3	Et	13	
4	i-Pr	14	
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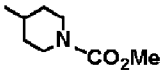
6		16	
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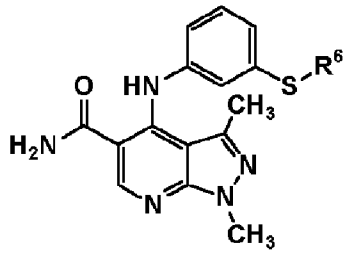
9		19	
10		20	

(0034)

Table 6



(I-B-1)

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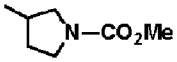
2	Me	12	
3	Et	13	
4	i-Pr	14	
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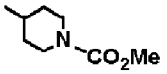
6		16	
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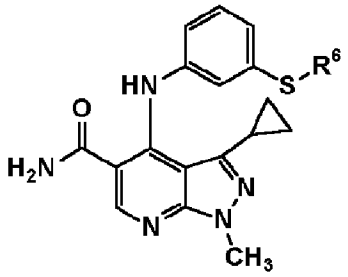
10		20	

(0035)

Table 7



(I-B-2)

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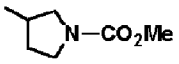
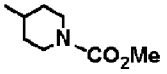
3	Et	13	
4	i-Pr	14	
5		15	
6		16	
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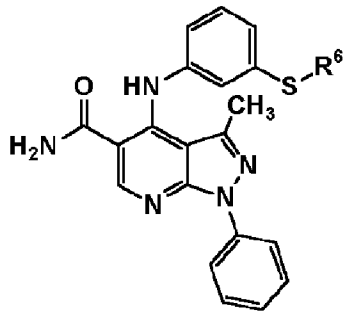
9		19	
10		20	

(0036)

Table 8



(I-B-3)

No.	R^6	No.	R^6
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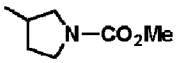
2	Me	12	
3	Et	13	
4	i-Pr	14	
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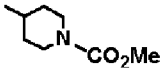
6		16	
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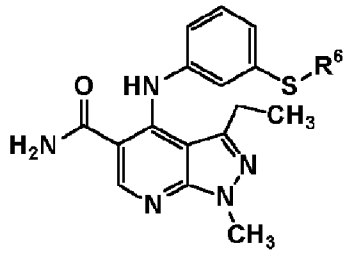
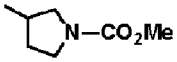
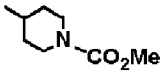
9		19	
10		20	

(0037)

Table 9



(I-B-4)

No.	R^6	No.	R^6
1	H	11	
2	Me	12	
3	Et	13	
4	i-Pr	14	
5		15	
6		16	
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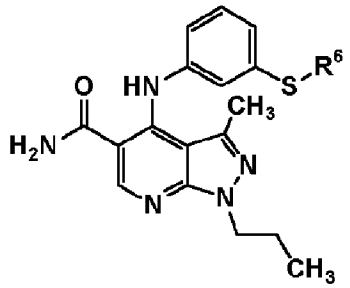
9		19	
10		20	

(0038)

Table 10



(I-B-5)

No.	R^6	No.	R^6
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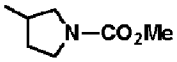
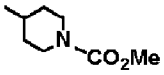
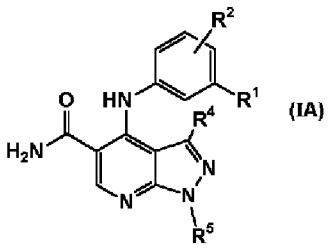
2	Me	12	
3	Et	13	
4	i-Pr	14	
5		15	
6		16	
7		17	
8		18	
9		19	
10		20	

(0039)

Processes for the Production of the Compounds of this Invention

The compounds represented by general formula (I) can be produced using a process in accordance with an Example or one of the following processes.

[1] Among the compounds of this invention represented by general formula (I), the compounds in which R^3 represents a hydrogen atom, namely the compound represented by general formula (IA)

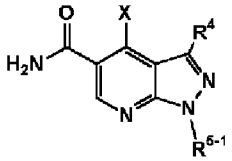


(IA)

(wherein, all the symbols have the same said definitions) can be produced using the following process.

(0040)

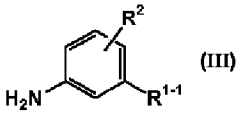
The compound represented by general formula (IA) is produced by reacting a compound represented by general formula (II),



(II)

(wherein, X denotes a halogen atom, and R^{1-1} and R^{5-1} respectively have the same meaning as R^1 and R^5, but when a hydroxy group, thiol group, amino group or carboxyl group which is included in the group represented by R^{1-1} and R^{5-1} requires protection, the said group is protected; all the other symbols have the same said meanings), with a compound represented by general formula (III),

(0041)



(III)

(wherein, all the symbols have the same said definitions), and thereafter in accordance with requirements subjecting the protecting group to a deprotecting reaction.

(0042)

The reaction of a compound represented by general formula (II) and a compound represented by general formula (III) is well known, and for example the reaction may be

carried out in an inert organic solvent (dimethyl formamide, dimethyl sulphoxide, chloroform, methylene chloride, diethyl ether, tetrahydrofuran, acetonitrile, dioxane or the like), in the presence or absence of base (triethylamine, pyridine and the like) at from 0° to the reflux temperature.

(0043)

The deprotecting reaction on the protecting group can be carried out using the following processes. Deprotecting reactions of protecting groups of carboxyl groups, hydroxy groups, amino groups and thiol groups are well known, and for example there may be included (1) alkaline hydrolysis, (2) deprotecting reactions under acidic conditions, (3) deprotecting reactions by hydrogenation and decomposition, (4) silyl group deprotecting reactions and the like.

(0044)

These processes will be described in more detail. (1) Deprotecting reactions by alkaline hydrolysis may be carried out for example in an organic solvent (methanol, tetrahydrofuran, dioxane or the like), using an hydroxide of an alkaline metal (sodium hydroxide, potassium hydroxide, lithium hydroxide or the like), a hydroxide of an alkaline earth metal (barium hydroxide, calcium hydroxide or the like) or a carbonate (sodium carbonate, potassium carbonate or the like), or an aqueous solution thereof or a mixture thereof, at a temperature of 0-40°C.

(0045)

(2) Deprotecting reactions under acidic conditions may be carried out, for example in an organic solvent (methylene chloride, chloroform, dioxane, ethyl acetate, anisole or the like), in an organic acid (acetic acid, trifluoroacetic acid, methane sulphonic acid or the like) or an inorganic acid (hydrochloric acid, sulphuric acid or the like) or a mixture thereof (hydrogen bromide / acetic acid and the like) at a temperature of 0-100°C.

(0046)

(3) Deprotecting reactions by hydrogenation and decomposition may be carried out, for example, in a solvent [an ether system (tetrahydrofuran, dioxane, dimethoxyethane, diethyl ether or the like), an alcohol system (methanol, ethanol and the like), a benzene system (benzene, toluene or the like), a ketone system (acetone, methyl ethyl ketone or the

like), a nitrile system (acetonitrile or the like), an amide system (dimethyl formamide or the like), water, ethyl acetate, acetic acid or a mixed solvent of two or more thereof or the like], in the presence of a catalyst (palladium-carbon, palladium black, palladium hydroxide, platinum oxide, Raney nickel or the like) in a hydrogen atmosphere at ambient pressure or under pressure, or in the presence of ammonium formate, and at a temperature of 0-200°C.

(0047)

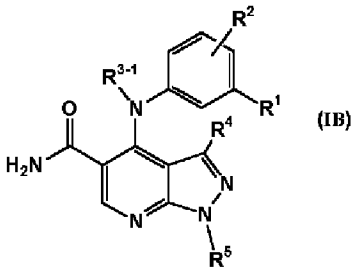
(4) Silyl group deprotecting reactions may be carried out for example in an organic solvent which is miscible with water (tetrahydrofuran, acetonitrile or the like) using tetrabutyl ammonium fluoride at a temperature of 0-40°C.

(0048)

Moreover, examples of a protecting group for carboxyl groups include a methyl group, ethyl group, t-butyl group, benzyl group and the like. Examples of a protecting group for hydroxy groups include a methoxymethyl group, 2-tetrahydropyranyl group, t-butyldimethyl silyl group, t-butyldiphenyl silyl group, acetyl group, benzyl group and the like. Examples of a protecting group for amino groups include a benzyloxy carbonyl group, t-butoxycarbonyl group, trifluoroacetyl group, 9-fluorenylmethoxycarbonyl group and the like. Examples of a protecting group for thiol groups include a benzyl group, methoxybenzyl group, methoxymethyl group, 2-tetrahydropyranyl group, diphenylmethyl group, acetyl group and the like. As long as the protecting group can be readily and selectively eliminated, the protecting group for carboxyl groups, hydroxy groups, amino groups or thiol groups is not limited to the aforesaid groups in particular. For example, the groups as described in T, W. Greene, Protective Groups in Organic Synthesis, Wiley, New York, 1991, can be used. Although it can be readily understood to a person skilled in the art, the target compound of this invention can be readily produced by selecting these deprotecting reactions.

(0049)

[2] Among the compounds represented by general formula (I), the compounds in which R^3 represents a C1-8 alkyl group, namely compounds represented by general formula (IB)



(IB)

(wherein, R^{3-1} denotes a C1-8 alkyl group, and the other symbols have the same aforesaid definitions), can be produced using the following process.

(0050)

The compounds represented by general formula (IB) can be produced by reacting the compound obtained by the reaction of a compound represented by said general formula (II) and a compound represented by general formula (III), with a compound represented by general formula (IV)

$$X\text{-}R^{3-1} \quad (IV)$$

(wherein, all the symbols have the same said definitions), and furthermore subjecting the protecting group to a deprotecting reaction in accordance with requirements.

(0051)

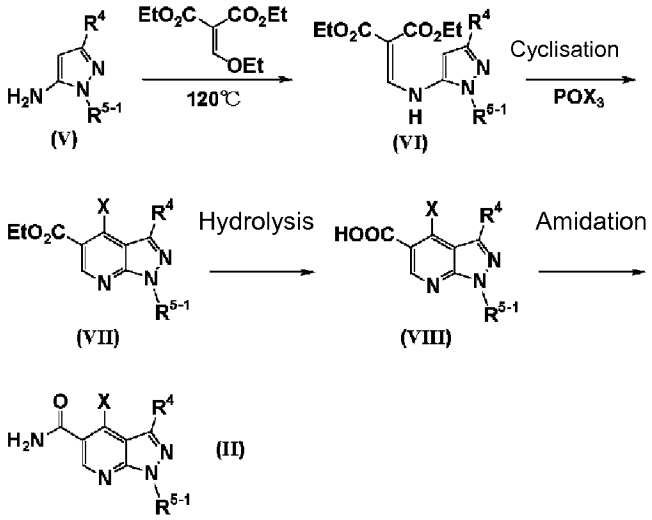
The reaction of a compound obtained by the reaction of a compound represented by said general formula (II) and a compound represented by general formula (III), with a compound represented by general formula (IV) is well known. For example, the reaction is carried out in an inert organic solvent (dimethyl formamide, dimethyl sulphoxide, chloroform, methylene chloride, tetrahydrofuran, acetonitrile, dioxane, toluene or the like) in the presence of a base (potassium carbonate, calcium carbonate, sodium carbonate, sodium hydroxide, potassium hydroxide, silver oxide or the like) at from 0°C to reflux temperature. The deprotecting reaction of the protecting group can be carried out in the same way as in the aforesaid processes.

(0052)

The compounds represented by general formula (II), (III) and (IV) used as starting materials are compounds which can be produced by well known methods or acquired as commercial products. For example, compounds represented by general formula (II) can be produced by the process shown in the Reaction Scheme 1.

(0053)

Reaction Scheme 1



In the Reaction Scheme Et denotes an ethyl group and the other symbols have the same said definitions.

(0054)

The compounds represented by general formula (V) in the reaction step are well known or can be readily produced by well known methods. In each reaction of this specification, the reaction product can be refined by an ordinary purification technique, for example, by distillation under reduced pressure or ambient pressure, high performance liquid chromatography using silica gel or magnesium silicate, thin layer chromatography, or column chromatography or a process such as washing, recrystallisation and the like. Purification may be carried out at each reaction or may be carried out after completion of all the reactions.

(0055)

Pharmacological effects

The compounds of this invention represented by general formula (I) have been proven to have PDE4 inhibiting activity by the following experiment.

In vitro enzyme assay

Experiment process

U937 cells (human monocyte derived) were cultured in a RPMI1640 culture medium containing 10 % fetal bovine serum. The U937 cells were recovered and homogenised with 20 mM Tris hydrochloric acid (Tris-HCl) [pH 8.0, PMSF (1 mM), leupeptin (1 μg/ml), pepstatin A (μg/ml) (sic)]. After centrifuging (at 15,000 rpm for 10 minutes), the supernatant liquid was recovered and was filtered with a 0.45 μm filter. A sample was loaded onto a MonoQ column (strong anion-exchange column, made by Pharmacia), and elution was carried out with a concentration gradient of 0-0.8 M of NaCl. The fraction in which the PDE activity was caused to disappear with 10 μM rolipram (PDE4 selective inhibitor) was recovered and used as an enzyme liquid for measuring the PDE4 inhibition activity.

(0056)

Enzyme activity measurements were carried out by the following process.

Diluted enzyme liquid (80 μl) (0.1 mg/kg bovine serum albumin-containing phosphate buffer (pH 7.4)), 10 μl of the compound of this invention (10 % DMSO) and 10 μl ^{3}H-cAMP (20,000 cpm, 10 μM) [imidazole buffer (100 mM, pH 7.5) containing $MgSO_4$ (100 mM) and bovine serum albumin (1 mg/ml)] were mixed together, and the mixture was incubated at room temperature for 30 minutes. The reaction was terminated by treating in a microwave oven for 2.5 mins. After centrifuging (2,000 rpm for one minute), 10 μl snake venom (1 mg/ml, made by Sigma Co., Product number V7000) was added and the mixture was incubated at room temperature for 30 minutes. Supernatant liquid (50 μl) was loaded onto an alumina column (100 μl), and elution was carried out with 80 μl of 0.005 N hydrochloric acid and the radioactivity of the eluate was measured.

(0057)

The PDE4 inhibiting activity rate of the compound of this invention was calculated using the following equation.

PDE4 activity inhibiting rate (%) = (1 - radioactivity in the presence of the compound of this invention / radioactivity in the absence of the compound of this invention) x 100.

(0058)

The IC_{50} value was calculated for each compound as the concentration of the compound of this invention to cause a 50 % inhibition of the PDE4 activity. The results of

the experiment are shown in Table 11.

(0059)

Table 11

Example Number	IC_{50} (μM)
1	0.004
1 (36)	0.003
1 (38)	0.010

(0060)

Toxicity

The toxicity of the compound of this invention represented by general formula (I) is extremely low and it is considered to be thoroughly safe for use as a drug.

(0061)

Application in Drugs

The compounds of this invention have PDE4 inhibitory activity, and therefore are thought to be useful for the prevention and/or treatment of inflammatory diseases (asthma, obstructive lung diseases, septicaemia, nephritis, hepatitis and the like), diabetic diseases, allergic diseases (allergic rhinitis, allergic conjunctivitis, atopic dermatitis and the like), autoimmune diseases (ulcerative colitis, Crohn's disease, rheumatism, psoriasis, multiple sclerosis, collagen disease and the like), osteoporosis, obesity, anti-depression (sic), Parkinson's disease, ischemic reperfusion disorders, leukaemia and the like.

(0062)

In order to use the compound represented by general formula (I), a non-toxic salt thereof or a solvate thereof in this invention with the said object, usually the compound is systemically or locally administered in oral or aoral form. The dosage differs depending on the age, body weight, symptoms, therapy effect, administration method, treatment time and the like, however usually the compound is orally administered once to several times per day per adult in a range of 1 mg -1000 mg per single administration, or the compound is administered aorally (preferably administered intravenously) once to several times per day per adult in a range of 1 mg - 100 mg per single administration, or the compound is

administered continuously intravenously in a range of from one hour to 24 hours per day. Of course, because the dosage changes depending on the various of conditions as described above, there may be cases in which a quantity lower than the aforesaid dosage is adequate, and moreover there may be case in which this dosage needs to be exceeded.

(0063)

When the compound represented by general formula (I) is administered, the compound is used as a solid composition, liquid composition or other composition for oral administration, or as an injection, topical agent or suppository for aoral administration. Solid compositions for oral administration include tablets, pills, capsule agents, powders, granules and the like. Capsule agents include hard capsules and soft capsules. In such a solid composition, one or more active materials is mixed with at least one inert diluent, for example lactose, mannitol, glucose, hydroxypropylcellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone or magnesium metasilicate aluminate. In accordance with normal methods, the composition may contain additives other than an inert diluent, for example a lubricant such as magnesium stearate, a disintegrating agent such as calcium carboxymethyl cellulose, a stabilising agent such as lactose and a solubiliser such as glutamic acid or aspartic acid. In accordance with requirements, tablets or pills may be coated with films of intestine soluble or stomach soluble substances such as refined sugar, gelatin, hydroxypropyl cellulose or hydroxypropyl methyl cellulose phthalate, and moreover tablets or pills may be coated with two or more layers thereof. Furthermore capsules of the substance which can be absorbed such as of gelatin are also included.

(0064)

Liquid compositions for oral administration include pharmaceutically acceptable emulsifiers, solvents, syrups, elixir agents and the like. In such liquid compositions, one or more active substances is contained in a conventionally used inert diluent (for example purified water or ethanol). These compositions may contain in addition to inert diluent, a wetting agent, an adjuvant such as a suspending agent, a sweetener, a flavouring agent, flavours and a preservative. As other compositions for oral administration, spray agents which contain one or more active substances and are formulated by a familiar process are included. These compositions may contain in addition to inert diluent, a stabiliser such as sodium bisulphite and a buffer agent to impart isotonicity for example an isotonic agent such as sodium chloride, citric acid or sodium citrate. A process for the production of a

spray agent is described in for example US Patent No. 2,868,691 and US Patent No. 3,095,355 in detail.

(0065)

As injection agents for aoral administration in accordance with this invention there are for example sterile aqueous and/or non-aqueous solvents, suspending agents and emulsifiers. As aqueous solvents and suspending agents, examples include distilled water for injection and physiological saline. As non-aqueous solvents and suspending agents, there are for example propylene glycol, polyethylene glycol, vegetable oils such as olive oil, alcohols such as ethanol, polysorbate 80 (Registered Trade Name) and the like. Moreover, sterile aqueous and non-aqueous solvents, suspending agents and emulsifiers may be mixed together and used. Furthermore such compositions may also include adjuvants such as a preservative, wetting agent, emulsifier, dispersant, stabilising agent (for example lactose) and solubiliser (for example glutamic acid, aspartic acid). These compositions may be sterilised by filtration through a bacteria retaining filter, formulation of a fungicide or irradiation. Also sterile solid compositions may be produced, wherein for example a freeze-dried product is dissolved in sterilised or sterile injectable distilled water or other solvent before use and this can be used. Other compositions for aoral administration include external solutions, ointments, liniments, suppositories for rectal administration and pessaries for intravaginal administration and the like containing one or more active substances formulated in accordance with conventional procedures.

(0066)

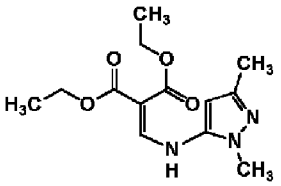
Reference Examples and Examples

Hereinafter, this invention will be explained in detail using Reference Examples and Examples, but it should be understood however that this invention is not restricted to these. The solvents in the brackets shown in the sections concerning separation by chromatography and TLC denote the eluting solvent or the developing solvent used, and the proportions given are by volume. The solvents in the brackets shown in the NMR sections denote the solvent used for the measurement.

(0067)

Reference Example 1

2-(((1,3-dimethylpyrazol-5-yl) amino) methylene) propane-1,3-dicarboxylic acid • diethyl ester.



(0068)

A mixture of 38.9 g ethoxymethylene malonic acid • diethyl ester and 20.0 g of 5-amino-1,3-dimethylpyrazole was stirred at a bath temperature of 120°C for one hour. The reaction mixture was cooled to room temperature, and next, 200 ml hexane was added. The produced crystals were dried after filtration, and 43.56 g of the title compound having the following physical property values was obtained.

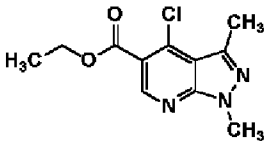
TLC: Rf 0.59 (chloroform : methanol = 10 : 1),

NMR ($CDCl_3$): δ 11.00 (bd, J = 12.3 Hz, 1H), 8.14 (d, J = 12.3 Hz, 1H), 5.86 (s, 1H), 4.32 (q, J = 7.2 Hz, 2H), 4.24 (q, J = 7.2 Hz, 2H), 3.74 (s, 3H), 2.23 (s, 3H), 1.38 (t, J = 7.2 Hz, 3H), 1.32 (t, J = 7.2 Hz, 3H).

(0069)

Reference Example 2

1,3-dimethyl-4-chloropyrazolo [5,4-b] pyridin-5-carboxylic acid • ethyl ester.



(0070)

A mixture of 43.56 g of the compound produced in Reference Example 1 and 144 ml phosphorus oxychloride was refluxed for five hours. The reaction mixture was cooled to room temperature, and thereafter discharged a little at a time into ice. After the generation of heat had subsided, water was added to make up to a total quantity of 3 litres, and thereafter the crude crystals were filtered off. The crude crystals were dissolved in 1 litre ethyl acetate, and the solution was successively washed with water and saturated aqueous

sodium chloride, dried with anhydrous magnesium sulphate and thereafter concentrated. Thereby 28.47 g of title compound having the following physical property values was obtained.

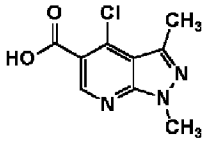
TLC: Rf 0.85 (chloroform : methanol = 10 : 1),

NMR ($CDCl_3$) : δ 8.95 (s, 1H), 4.45 (q, J = 7.2 Hz, 2H), 4.07 (s, 3H), 2.76 (s, 3H), 1.43 (t, J = 7.2 Hz, 3H).

(0071)

Reference Example 3

1,3-dimethyl-4-chloropyrazolo [5,4-b] pyridin-5-carboxylic acid.



(0072)

To a 225 ml dimethoxyethane solution of 28.47 g of the compound produced in Reference Example 2, was added 59.15 g of 85 % potassium hydroxide, and thereafter thereto was added dropwise 180 ml water, and the mixture was stirred at room temperature overnight. The reaction mixture was neutralised with 225 ml of 4 N - hydrochloric acid while cooling. The produced crystals were filtered, washed with water and thereafter dried, and 25.25 g of the title compound having the following physical property values was obtained.

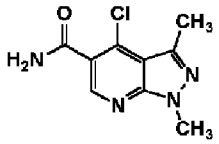
TLC: Rf 0.10 (chloroform : methanol = 10 : 1),

NMR (DMSO- d_6): δ 8.90 (s, 1H), 3.99 (s, 3H), 3.34 (bs, 1H), 2.67 (s, 3H).

(0073)

Reference Example 4

1,3-dimethyl-4-chloro pyrazolo [5,4-b] pyridin-5-carboxamide.



(0074)

A mixture of 15.79 g of the compound produced in Reference Example 3 and 25.5 ml of thionyl chloride was refluxed for one hour, and the mixture was concentrated under vacuum. A 140 ml tetrahydrofuran solution of the obtained residue was added dropwise under ice cooling to a mixed solution of 238 ml tetrahydrofuran and 95 ml of 28 % ammonium hydroxide aqueous solution and the mixture was stirred for 30 minutes. The produced crystals were filtered, washed with water and thereafter dried, and 14.69 g of the title compound having the following physical property values was thereby obtained.

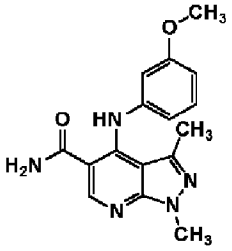
TLC: Rf 0.45 (chloroform : methanol = 10 : 1),

NMR (DMSO-d_6): δ 8.54 (s, 1H), 8.03 (bs, 1H), 7.79 (bs, 1H), 3.99 (s, 3H), 2.66 (s, 3H).

(0075)

Example 1.

1,3-dimethyl-4-(3-methoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0076)

A 10 ml dioxane solution of 702 mg of the compound produced in Reference Example 4 and 1.15 g of 3-methoxyaniline was refluxed for six hours, and the mixture was concentrated under vacuum. The obtained residue was dissolved in a mixed solvent of 70 ml ethyl acetate and 30 ml tetrahydrofuran, and the solution was washed successively with water and saturated aqueous sodium chloride, dried with anhydrous magnesium sulphate, and thereafter concentrated. The crude purified material was recrystallised from dioxane, and 774 mg of the compound of this invention having the following physical property values was thereby obtained.

TLC: Rf 0.32 (chloroform : methanol = 10 : 1),

NMR (DMSO-d_6): δ 10.97 (s, 1H), 8.74 (s, 1H), 8.21 (bs, 1H), 7.56 (bs, 1H), 7.26-7.17

(m, 1H), 6.75-6.60 (m, 3H), 3.89 (s, 3H), 3.71 (s, 3H), 1.69 (s, 3H).

(0077)

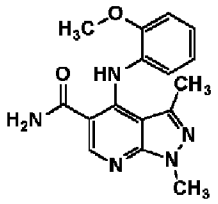
Example 1 (1) - Example 1 (69).

The compound produced in Reference Example 4 or corresponding halogen derivatives thereof, and 3-methoxyaniline or the corresponding amine derivatives were subjected to the same procedures as in Example 1. The following compounds of this invention were thereby obtained.

(0078)

Example 1 (1)

1,3-dimethyl-4-(2-methoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0079)

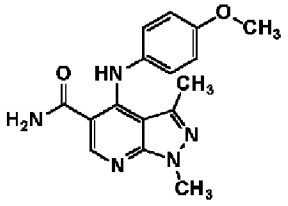
TLC: Rf 0.32 (chloroform : methanol = 10 : 1),

NMR (DMSO-d_6): δ 10.70 (s, 1H), 8.71 (s, 1H), 8.18 (bs, 1H), 7.49 (bs, 1H), 7.16-7.08 (m, 2H), 6.95 (d, J = 7.5 Hz, 1H), 6.88-6.79 (m, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 1.59 (s, 3H).

(0080)

Example 1 (2)

1,3-dimethyl-4-(4-methoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0081)

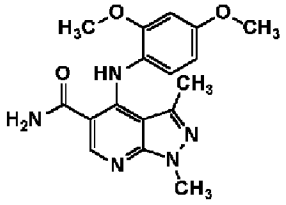
TLC: Rf 0.32 (chloroform : methanol = 10 : 1),

NMR (DMSO-d_6): δ 11.11 (s, 1H), 8.71 (s, 1H), 8.16 (bs, 1H), 7.49 (bs, 1H), 7.08 (d, J = 6.9 Hz, 2H), 6.92 (d, J = 6.9 Hz, 2H), 3.85 (s, 3H), 3.75 (s, 3H), 1.54 (s, 3H).

(0082)

Example 1 (3)

1,3-dimethyl-4-(2,4-dimethoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0083)

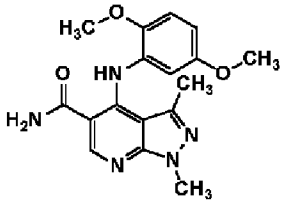
TLC: Rf 0.32 (chloroform : methanol = 10 : 1),

NMR (DMSO-d_6): δ 10.81 (s, 1H), 8.66 (s, 1H), 8.11 (bs, 1H), 7.42 (bs, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.69 (d, J = 2.7 Hz, 1H), 6.44 (dd, J = 8.4, 2.7 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.76 (s, 3H), 1.53 (s, 3H).

(0084)

Example 1 (4)

1,3-dimethyl-4-(2,5-dimethoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0085)

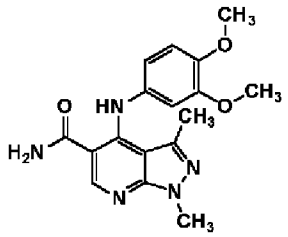
TLC: Rf 0.32 (chloroform : methanol = 10 : 1),

NMR (DMSO-d_6): δ 11.03 (s, 1H), 8.75 (s, 1H), 8.29 (bs, 1H), 7.61 (bs, 1H), 7.04 (d, J = 9.0 Hz, 1H), 6.72 (dd, J = 9.0, 3.0 Hz, 1H), 6.59 (d, J = 3.0 Hz, 1H), 3.91 (s, 3H), 3.78 (s, 3H), 3.59 (s, 3H), 1.66 (s, 3H).

(0086)

Example 1 (5)

1,3-dimethyl-4-(3,4-dimethoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0087)

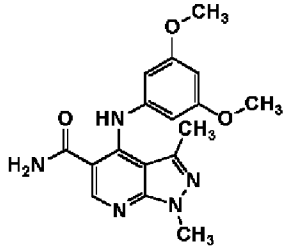
TLC: Rf 0.32 (chloroform : methanol = 10 : 1),

NMR (DMSO-d_6): δ 11.12 (s, 1H), 8.70 (s, 1H), 8.17 (bs, 1H), 7.49 (bs, 1H), 6.88 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 2.4 Hz, 1H), 6.61 (dd, J = 8.4, 2.4 Hz, 1H), 3.86 (s, 3H), 3.73 (s, 3H), 3.69 (s, 3H), 1.59 (s, 3H).

(0088)

Example 1 (6)

1,3-dimethyl-4-(3,5-dimethoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0089)

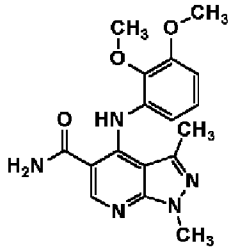
TLC: Rf 0.32 (chloroform : methanol = 10 : 1),

NMR (DMSO-d_6): δ 10.90 (s, 1H), 8.73 (s, 1H), 8.20 (bs, 1H), 7.55 (bs, 1H), 6.26 (s, 1H), 6.25 (s, 2H), 3.89 (s, 3H), 3.67 (s, 6H), 1.79 (s, 3H).

(0090)

Example 1 (7)

1,3-dimethyl-4-(2,3-dimethoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0091)

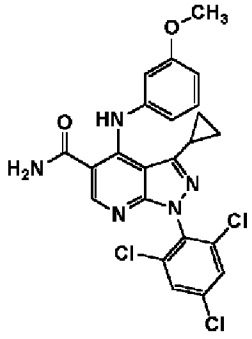
TLC: Rf 0.32 (chloroform : methanol = 10 : 1),

NMR (DMSO-d_6): δ 11.17 (bs, 1H), 8.78 (s, 1H), 8.32 (bs, 1H), 7.65 (bs, 1H), 6.96 (t, J = 8.1 Hz, 1H), 6.86 (dd, J = 8.1, 1.5 Hz, 1H), 6.64 (dd, J = 8.1, 1.5 Hz, 1H), 3.92 (s, 3H), 3.84 (s, 3H), 3.75 (s, 3H), 1.71 (s, 3H).

(0092)

Example 1 (8)

1-(2,4,6-trichlorophenyl)-3-cyclopropyl-4-(3-methoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0093)

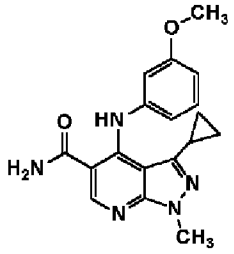
TLC: Rf 0.33 (ethyl acetate : hexane = 1:1),

NMR (DMSO-d_6): δ 10.94 (s, 1H), 8.67 (s, 1H), 8.25 (bs, 1H), 7.97 (s, 2H), 7.65 (bs, 1H), 7.25 (t, J = 7.8 Hz, 1H), 6.76-6.64 (m, 3H), 3.69 (s, 3H), 1.35-1.20 (m, 1H), 0.72-0.63 (m, 2H), 0.52-0.43 (m, 2H).

(0094)

Example 1 (9)

1-methyl-3-cyclopropyl-4-(3-methoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0095)

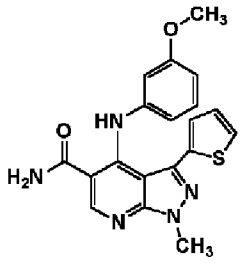
TLC: Rf 0.33 (ethyl acetate),

NMR (DMSO-d_6): δ 11.00 (s, 1H), 8.74 (s, 1H), 8.22 (bs, 1H), 7.57 (bs, 1H), 7.19 (t, J = 7.8 Hz, 1H), 6.69-6.60 (m, 3H), 3.87 (s, 3H), 3.68 (s, 3H), 1.26-1.14 (m, 1H), 0.70-0.60 (m, 2H), 0.44-0.34 (m, 2H).

(0096)

Example 1 (10)

1-methyl-3-(thiophen-2-yl)-4-(3-methoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0097)

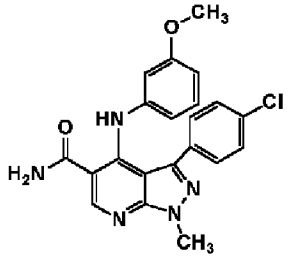
TLC: Rf 0.36 (ethyl acetate),

NMR (DMSO-d_6): δ 11.12(1H), 8.84 (s, 1H), 8.29 (bs, 1H), 7.66 (bs, 1H), 7.25 (dd, J = 5.1, 0.9 Hz, 1H), 6.92 (dd, J = 3.6, 0.9 Hz, 1H), 6.81 (t, J = 7.5 Hz, 1H), 6.66 (dd, J = 5.1, 3.6 Hz, 1H), 6.37-6.24 (m, 3H), 4.04 (s, 3H), 3.55 (s, 3H).

(0098)

Example 1 (11)

1-methyl-3-(4-chlorophenyl)-4-(3-methoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0099)

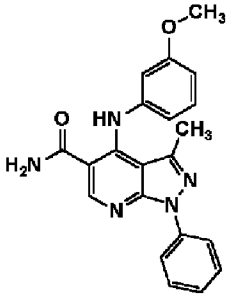
TLC: Rf 0.35 (ethyl acetate),

NMR (DMSO-d_6): δ 11.22 (s, 1H), 8.85 (s, 1H), 8.30 (bs, 1H), 7.65 (bs, 1H), 7.26 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H), 6.80-6.70 (m, 1H), 6.28-6.20 (m, 3H), 4.04 (s, 3H), 3.54 (s, 3H).

(0100)

Example 1 (12)

1-phenyl-3-methyl-4-(3-methoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0101)

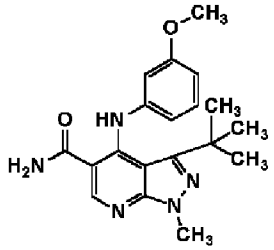
TLC: Rf 0.43 (chloroform : methanol = 9 : 1),

NMR ($CDCl_3$) : δ 10.56 (s, 1H), 8.60 (s, 1H), 8.12-8.09 (m, 2H), 7.53-7.48 (m, 2H), 7.26-7.18 (m, 2H), 6.78-6.69 (m, 3H), 5.90-5.70 (brs, 2H), 3.77 (s, 3H), 1.77 (s, 3H).

(0102)

Example 1 (13)

1-methyl-3-t-butyl-4-(3-methoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0103)

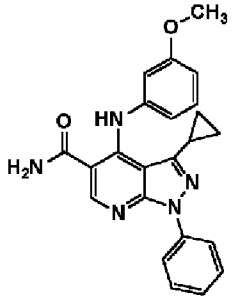
TLC: Rf 0.30 (ethyl acetate),

NMR (DMSO-d_6): δ 8.62 (s, 1H), 8.14 (s, 1H), 7.73 (bs, 1H), 7.39 (bs, 1H), 7.03 (t, J = 8.4 Hz, 1H), 6.43-6.35 (m, 1H), 6.27-6.20 (m, 2H), 3.99 (s, 3H), 3.64 (s, 3H), 1.33 (s, 9H).

(0104)

Example 1 (14)

1-phenyl-3-cyclopropyl-4-(3-methoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0105)

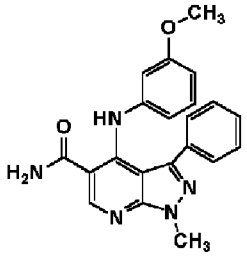
TLC: Rf 0.44 (chloroform : methanol = 9 : 1),

NMR ($CDCl_3$) : δ 10.50 (s, 1H), 8.61 (s, 1H), 8.12 (t, J = 7.5 Hz, 2H), 7.49 (t, J = 8.1 Hz, 2H), 7.31-7.17 (m, 2H), 6.78-6.62 (m, 3H), 6.00-5.60 (brs, 2H), 1.37-1.25 (m, 1H), 0.90-0.81 (m, 2H), 0.53-0.48 (m, 2H).

(0106)

Example 1 (15)

1-methyl-3-phenyl-4-(3-methoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0107)

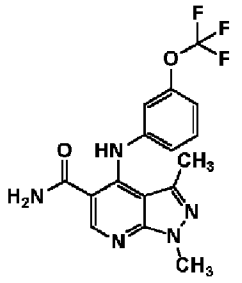
TLC: Rf 0.46 (chloroform : methanol = 9 : 1),

NMR ($CDCl_3$) : δ 10.47 (s, 1H), 8.64 (s, 1H), 7.35-7.31 (m, 2H), 7.11-7.06 (m, 3H), 6.75 (t, J = 8.1 Hz, 1H), 6.37-6.32 (m, 1H), 6.26-6.19 (m, 2H), 5.90-5.75 (brs, 2H), 4.14 (s, 3H), 3.59 (s, 3H).

(0108)

Example 1 (16)

1,3-dimethyl-4-(3-trifluoromethoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0109)

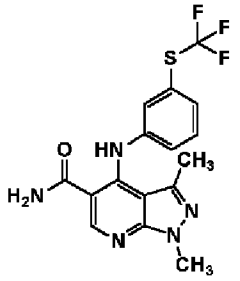
TLC: Rf 0.30 (ethyl acetate),

NMR (DMSO-d_6): δ 10.97 (s, 1H), 8.78 (s, 1H), 8.26 (bs, 1H), 7.62 (bs, 1H), 7.48-7.37 (m, 1H), 7.16-7.05 (m, 3H), 3.92 (s, 3H), 1.71 (s, 3H).

(0110)

Example 1 (17)

1,3-dimethyl-4-(3-trifluoromethylthiophenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0111)

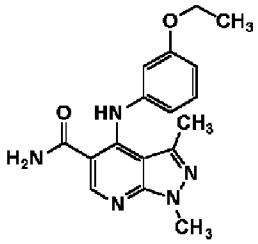
TLC: Rf 0.30 (ethyl acetate),

NMR (DMSO-d_6): δ 11.04 (s, 1H), 8.79 (s, 1H), 8.29 (bs, 1H), 7.63 (bs, 1H), 7.54-7.32 (m, 4H), 3.92 (s, 3H), 1.66 (s, 3H).

(0112)

Example 1 (18)

1,3-dimethyl-4-(3-ethoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0113)

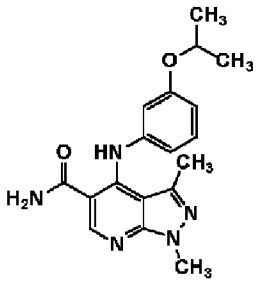
TLC: Rf 0.36 (chloroform : methanol = 9 : 1),

NMR ($CDCl_3$) : δ 10.58 (s, 1H), 8.52 (s, 1H), 7.21-7.15 (m, 1H), 6.72-6.65 (m, 3H), 5.85-5.60 (brs, 2H), 3.99 (s, 3H), 3.97 (q, J = 6.9 Hz, 2H), 1.77 (s, 3H), 1.37 (t, J = 6.9 Hz, 3H).

(0114)

Example 1 (19)

1,3-dimethyl-4-(3-isopropyloxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0115)

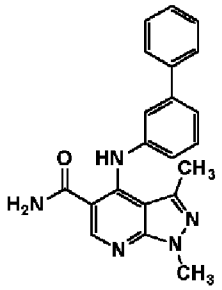
TLC: Rf 0.41 (chloroform : methanol = 9 : 1),

NMR ($CDCl_3$) : δ 10.58 (s, 1H), 8.52 (s, 1H), 7.20-7.13 (m, 1H), 6.72-6.65 (m, 3H), 5.85-5.60 (brs, 2H), 4.48 (sept, J = 6.0 Hz, 1H), 3.99 (s, 3H), 1.77 (s, 3H), 1.29 (d, J = 6.0 Hz, 6H).

(0116)

Example 1 (20)

1,3-dimethyl-4-(3-phenylphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0117)

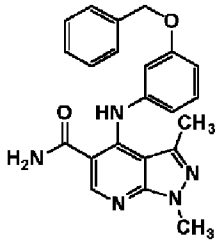
TLC: Rf 0.32 (chloroform : methanol = 9 : 1),

NMR (DMSO-d_6): δ 11.10 (s, 1H), 8.75 (s, 1H), 8.30-8.10 (brs, 1H), 7.60-7.57 (m, 3H), 7.45-7.34 (m, 6H), 7.13-7.04 (m, 1H), 3.88 (s, 3H), 1.66 (s, 3H).

(0118)

Example 1 (21)

1,3-dimethyl-4-(3-benzyloxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0119)

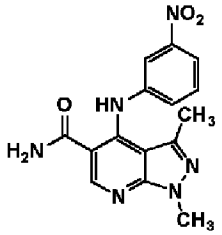
TLC: Rf 0.28 (chloroform : methanol = 9 : 1),

NMR (DMSO-d_6): δ 10.94 (s, 1H), 8.72 (s, 1H), 8.23-8.10 (brs, 1H), 7.60-7.50 (brs, 1H), 7.40-7.29 (m, 5H), 7.19 (t, J = 8.7 Hz, 1H), 6.78-6.75 (m, 2H), 6.64 (d, J = 8.7 Hz, 1H), 5.06 (s, 2H), 3.87 (s, 3H), 1.64 (s, 3H).

(0120)

Example 1 (22)

1,3-dimethyl-4-(3-nitrophenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0121)

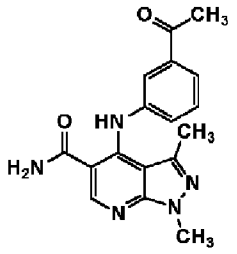
TLC: Rf 0.28 (chloroform : methanol = 9 : 1),

NMR (DMSO-d_6): δ 10.81 (s, 1H), 8.77 (s, 1H), 8.24 (brs, 1H), 7.90-7.84 (m, 2H), 7.62 (brs, 1H), 7.58-7.46 (m, 2H), 3.93 (s, 3H), 1.80 (s, 3H).

(0122)

Example 1 (23)

1,3-dimethyl-4-(3-acetylphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0123)

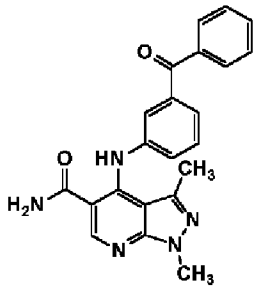
TLC: Rf 0.30 (ethyl acetate),

NMR (DMSO-d_6): δ 11.00 (s, 1H), 8.77 (s, 1H), 8.24 (bs, 1H), 7.70 (d, J = 7.5 Hz, 1H), 7.63 (s, 1H), 7.59 (bs, 1H), 7.46 (t, J = 7.5 Hz, 1H), 7.35 (d, J = 7.5 Hz, 1H), 3.91 (s, 3H), 2.54 (s, 3H), 1.65 (s, 3H).

(0124)

Example 1 (24)

1,3-dimethyl-4-(3-benzoylphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0125)

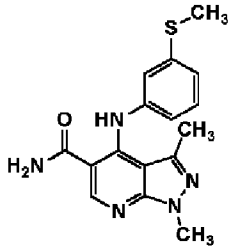
TLC: Rf 0.30 (ethyl acetate),

NMR (DMSO-d_6): δ 10.94 (s, 1H), 8.75 (s, 1H), 8.22 (bs, 1H), 7.70-7.62 (m, 3H), 7.59 (bs, 1H), 7.54-7.40 (m, 5H), 7.36-7.31 (m, 1H), 3.93 (s, 3H), 1.76 (s, 3H).

(0126)

Example 1 (25)

1,3-dimethyl-4-(3-methylthiophenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0127)

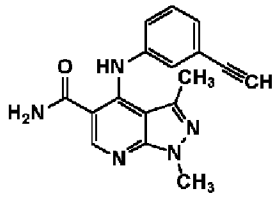
TLC: Rf 0.30 (ethyl acetate),

NMR (DMSO-d_6): δ 10.98 (s, 1H), 8.74 (s, 1H), 8.22 (bs, 1H), 7.56 (bs, 1H), 7.23 (t, J = 8.1 Hz, 1H), 7.01 (s, 1H), 7.00 (d, J = 8.1 Hz, 1H), 6.84 (d, J = 8.1 Hz, 1H), 3.89 (s, 3H), 2.42 (s, 3H), 1.69 (s, 3H).

(0128)

Example 1 (26)

1,3-dimethyl-4-(3-ethinylphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0129)

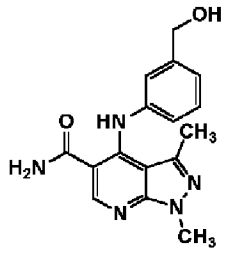
TLC: Rf 0.22 (chloroform : methanol = 9 : 1),

NMR (DMSO-d_6): δ 10.91 (s, 1H), 8.75 (s, 1H), 8.25 (s, 1H), 7.60 (brs, 1H), 7.10-7.35 (m, 4H), 4.17 (s, 1H), 3.89 (s, 3H), 1.67 (s, 3H).

(0130)

Example 1 (27)

1,3-dimethyl-4-(3-hydroxymethylphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0131)

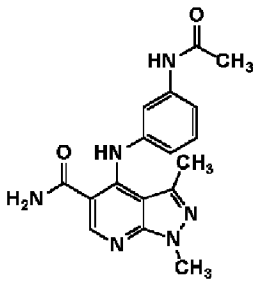
TLC: Rf 0.65 (chloroform : methanol = 9 : 1),

NMR (DMSO-d_6): δ 11.05 (s, 1H), 8.73 (s, 1H), 8.20 (br, 1H), 7.54 (br, 1H), 7.26 (dd, J = 8.0, 8.0 Hz, 1H), 7.08-7.03 (m, 2H), 6.96 (d, J = 8.0 Hz, 1H), 5.16 (t, J = 6.2 Hz, 1H), 4.42 (d, J = 6.2 Hz, 2H), 3.87 (s, 3H), 1.61 (s, 3H).

(0132)

Example 1 (28)

1,3-dimethyl-4-(3-acetylaminophenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0133)

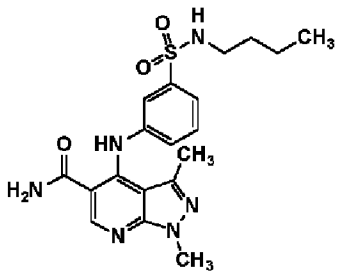
TLC: Rf 0.20 (chloroform : methanol = 9 : 1),

NMR (DMSO-d_6): δ 10.99 (s, 1H), 9.88 (s, 1H), 8.73 (s, 1H), 8.22 (brs, 1H), 7.57 (brs, 1H), 7.35-7.32 (m, 2H), 7.22 (t, J = 8.1 Hz, 1H), 6.78 (d, J = 8.1 Hz, 1H), 3.87 (s, 3H), 1.97 (s, 3H), 1.66 (s, 3H).

(0134)

Example 1 (29)

1,3-dimethyl-4-(3-butylsulphamoylphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0135)

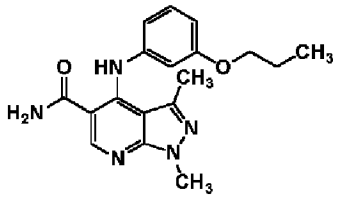
TLC: Rf 0.25 (chloroform : methanol = 9 : 1),

NMR (DMSO-d_6): δ 11.14 (s, 1H), 8.80 (s, 1H), 8.35 (brs, 1H), 7.67 (brs, 1H), 7.57 (brs, 1H), 7.60-7.37 (m, 4H), 3.91 (s, 3H), 2.63 (q, J = 7.2 Hz, 2H), 1.65 (s, 3H), 1.35-1.15 (m, 4H), 0.78 (t, J = 7.2 Hz, 3H).

(0136)

Example 1 (30)

1,3-dimethyl-4-(3-propoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0137)

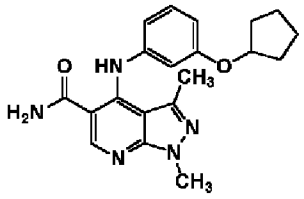
TLC: Rf 0.36 (ethyl acetate),

NMR (DMSO-d_6): δ 10.96 (s, 1H), 8.74 (s, 1H), 8.20 (bs, 1H), 7.55 (bs, 1H), 7.19 (t, J = 8.4 Hz, 1H), 6.74-6.68 (m, 1H), 6.67 (s, 1H), 6.63 (d, J = 8.4 Hz, 1H), 3.89 (s, 3H), 3.87 (t, J = 6.9 Hz, 2H), 1.69 (s, 3H), 1.68 (sext, J = 6.9 Hz, 2H), 0.94 (t, J = 6.9 Hz, 3H).

(0138)

Example 1 (31)

1,3-dimethyl-4-(3-cyclopentyloxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0139)

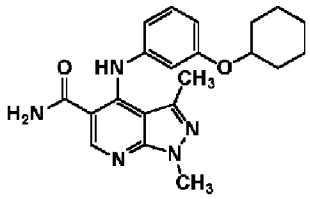
TLC: Rf 0.35 (ethyl acetate),

NMR (DMSO-d_6): δ 10.98 (s, 1H), 8.74 (s, 1H), 8.21 (bs, 1H), 7.56 (bs, 1H), 7.19 (t, J = 8.4 Hz, 1H), 6.70-6.60 (m, 3H), 4.80-4.72 (m, 1H), 3.89 (s, 3H), 1.90-1.46 (m, 8H), 1.68 (s, 3H).

(0140)

Example 1 (32)

1,3-dimethyl-4-(3-cyclohexyloxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0141)

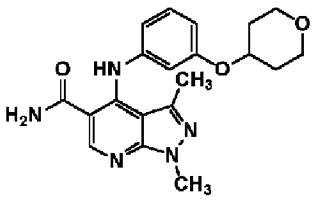
TLC: Rf 0.52 (ethyl acetate),

NMR (DMSO-d_6): δ 11.05 (br, 1H), 8.74 (s, 1H), 8.23 (br, 1H), 7.58 (br, 1H), 7.18 (dd, J = 8.1, 8.1 Hz, 1H), 6.73-6.61 (m, 3H), 4.32-4.23 (m, 1H), 3.88 (s, 3H), 1.90-1.81 (m, 2H), 1.72-1.59 (m, 1H), 1.66 (s, 3H), 1.54-1.43 (m, 1H), 1.43-1.13 (m, 6H).

(0142)

Example 1 (33)

1,3-dimethyl-4-(3-(2H-3, 4, 5, 6-tetrahydropyran-4-yl) oxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0143)

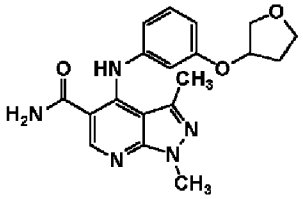
TLC: Rf 0.40 (ethyl acetate),

NMR (DMSO-d_6): δ 11.11 (br, 1H), 8.75 (s, 1H), 8.25 (br, 1H), 7.60 (br, 1H), 7.23-7.17 (m, 1H), 6.78-6.75 (m, 2H), 6.66 (d, J = 7.8 Hz, 1H), 4.58-4.48 (m, 1H), 3.89 (s, 3H), 3.84-3.76 (m, 2H), 3.47-3.38 (m, 2H), 1.95-1.85 (m, 2H), 1.65 (s, 3H), 1.58-1.45 (m, 2H).

(0144)

Example 1 (34)

1,3-dimethyl-4-(3-(oxolan-3-yl) oxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0145)

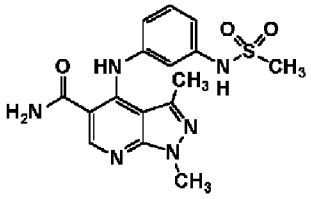
TLC: Rf 0.32 (ethyl acetate),

NMR ($CDCl_3$) : δ 10.59 (s, 1H), 8.53 (s, 1H), 7.23-7.15 (m, 1H), 6.77-6.71 (m, 1H), 6.67-6.61 (m, 2H), 5.83 (bs, 2H), 4.90-4.82 (m, 1H), 3.99 (s, 3H), 3.98-3.83 (m, 4H), 2.23-2.04 (m, 2H), 1.77 (s, 3H).

(0146)

Example 1 (35)

1,3-dimethyl-4-(3-(methylsulphonylamino) phenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0147)

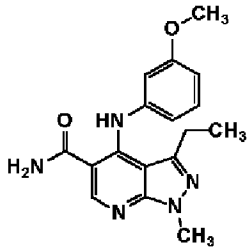
TLC: Rf 0.30 (methylene chloride : methanol = 10:1),

NMR (DMSO-d_6): δ 10.96 (s, 1H), 9.72 (s, 1H), 8.75 (s, 1H), 8.23 (bs, 1H), 7.59 (bs, 1H), 7.27 (t, J = 8.1 Hz, 1H), 7.00-6.92 (m, 2H), 6.87-6.81 (m, 1H), 3.89 (s, 3H), 2.94 (s, 3H), 1.70 (s, 3H).

(0148)

Example 1 (36)

1-methyl-3-ethyl-4-(3-methoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0149)

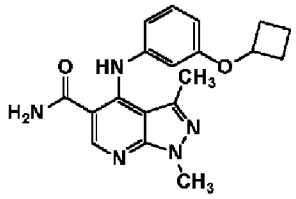
TLC: Rf 0.59 (ethyl acetate),

NMR (DMSO-d_6): δ 10.87 (s, 1H), 8.74 (s, 1H), 8.21 (br., s, 1H), 7.56 (br., s, 1H), 7.17 (t, J = 8.1 Hz, 1H), 6.70-6.60 (m, 2H), 6.58 (m, 1H), 3.90 (s, 3H), 3.68 (s, 3H), 1.98 (q, J = 7.2 Hz, 2H), 0.93 (t, J = 7.2 Hz, 3H).

(0150)

Example 1 (37)

1,3-dimethyl-4-(3-cyclobutyloxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0151)

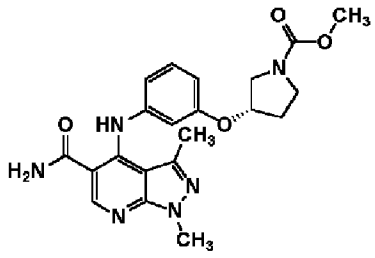
TLC: Rf 0.50 (toluene : ethyl acetate = 1 : 20),

NMR (DMSO-d_6): δ 11.08 (br, 1H), 8.74 (s, 1H), 8.25 (br, 1H), 7.60 (br, 1H), 7.19 (dd, J = 8.0, 8.0 Hz, 1H), 6.68-6.56 (m, 3H), 4.61 (quintet, J = 7.1 Hz, 1H), 3.88 (s, 3H), 2.35-2.23 (m, 2H), 2.03-1.85 (m, 2H), 1.79-1.64 (m, 1H), 1.89 (s, 3H), 1.64-1.49 (m, 1H).

(0152)

Example 1 (38)

1,3-dimethyl-4-(3-((3S)-1-methoxycarbonylpyrrolidin-3-yloxy) phenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0153)

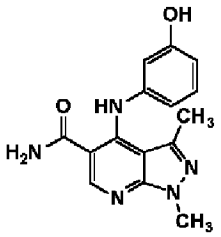
TLC: Rf 0.55 (ethyl acetate : methanol = 10 : 1),

NMR (DMSO-d_6): δ 10.93 (br, 1H), 8.73 (s, 1H), 8.19 (br, 1H), 7.55 (br, 1H), 7.20 (dd, J = 8.4, 8.4 Hz, 1H), 6.72-6.63 (m, 3H), 4.99 (m, 1H), 3.87 (s, 3H), 3.57&3.56 (s, 3H), 3.53-3.27 (m, 4H), 2.18-1.95 (m, 2H), 1.68 (s, 3H).

(0154)

Example 1 (39)

1,3-dimethyl-4-(3-hydroxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0155)

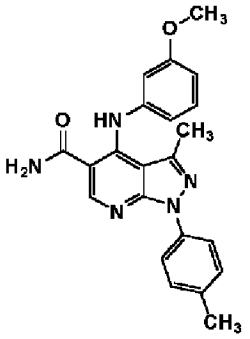
TLC: Rf 0.27 (chloroform : methanol = 10 : 1),

NMR (DMSO-d_6): δ 10.91 (s, 1H), 9.43 (s, 1H), 8.72 (s, 1H), 8.20 (br., s, 1H), 7.54 (br., s, 1H), 7.09 (t, J = 7.8 Hz, 1H), 6.55-6.45 (m, 3H), 3.87 (s, 3H), 1.70 (s, 3H).

(0156)

Example 1 (40)

1-(4-methylphenyl)-3-methyl-4-(3-methoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0157)

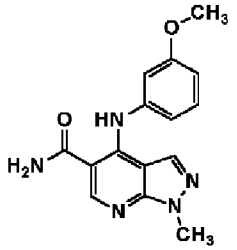
TLC: Rf 0.60 (chloroform : methanol = 9 : 1),

NMR (DMSO-d_6): δ 10.91 (s, 1H), 8.79 (s, 1H), 8.26 (brs, 1H), 8.03 (d, J = 8.1 Hz, 2H), 7.66 (brs, 1H), 7.31 (d, J = 8.1 Hz, 2H), 7.21 (t, J = 8.4 Hz, 1H), 6.75-6.67 (m, 3H), 3.71 (s, 3H), 2.35 (s, 3H), 1.79 (s, 3H).

(0158)

Example 1 (41)

1-methyl-4-(3-methoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0159)

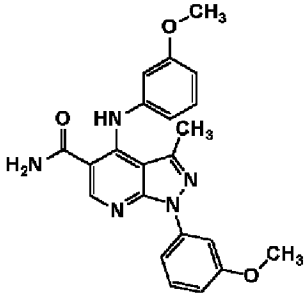
TLC: Rf 0.31 (ethyl acetate),

NMR (DMSO-d_6): δ 11.49 (s, 1H), 8.72 (s, 1H), 8.14 (br., s, 1H), 7.46 (br., s, 1H), 7.38 (t, J = 7.5 Hz, 1H), 7.00-6.85 (m, 3H), 6.67 (s, 1H), 3.89 (s, 3H), 3.75 (s, 3H).

(0160)

Example 1 (42)

1-(3-methoxyphenyl)-3-methyl-4-(3-methoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0161)

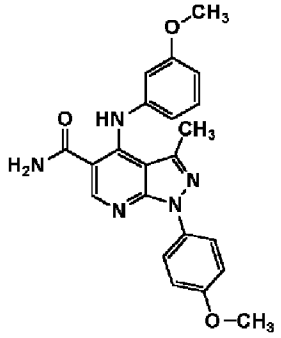
TLC: Rf 0.36 (chloroform : methanol = 9 : 1),

NMR (DMSO-d_6): δ 10.92 (s, 1H), 8.82 (s, 1H), 8.35-8.20 (brs, 1H), 7.82-7.79 (m, 2H), 7.73-7.60 (brs, 1H), 7.42 (t, J = 8.1 Hz, 1H), 7.22 (t, J = 8.1 Hz, 1H), 6.89-6.85 (m, 1H), 6.75-6.68 (m, 3H), 3.82 (s, 3H), 3.71 (s, 3H), 1.80 (s, 3H).

(0162)

Example 1 (43)

1-(4-methoxyphenyl)-3-methyl-4-(3-methoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0163)

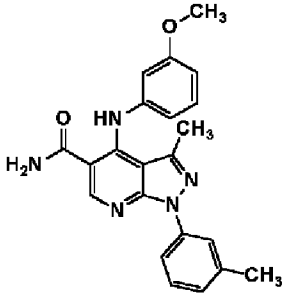
TLC: Rf 0.46 (chloroform : methanol = 9 : 1),

NMR (DMSO-d_6): δ 10.93 (s, 1H), 8.78 (s, 1H), 8.30-8.20 (brs, 1H), 8.00 (d, J = 9.0 Hz, 2H), 7.67-7.58 (brs, 1H), 7.22 (t, J = 8.1 Hz, 1H), 7.08 (d, J = 9.0 Hz, 2H), 6.75-6.67 (m, 3H), 3.80 (s, 3H), 3.71 (s, 3H), 1.79 (s, 3H).

(0164)

Example 1 (44)

1-(3-methylphenyl)-3-methyl-4-(3-methoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0165)

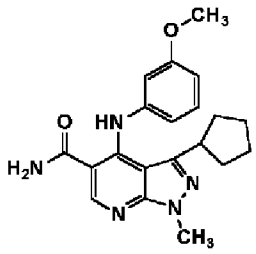
TLC: Rf 0.45 (chloroform : methanol = 9 : 1),

NMR (DMSO-d_6): δ 10.92 (s, 1H), 8.81 (s, 1H), 8.26 (brs, 1H), 8.00-7.95 (m, 2H), 7.67 (brs, 1H), 7.40 (t, J = 7.8 Hz, 1H), 7.21 (t, J = 7.8 Hz, 1H), 7.12 (d, J = 7.8 Hz, 1H), 6.80-6.65 (m, 3H), 3.71 (s, 3H), 2.39 (s, 3H), 1.80 (s, 3H).

(0166)

Example 1 (45)

1-methyl-3-cyclopentyl-4-(3-methoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0167)

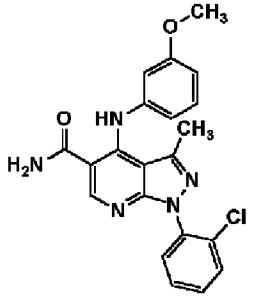
TLC: Rf 0.50 (chloroform : methanol = 10 : 1),

NMR (DMSO-d_6): δ 10.82 (s, 1H), 8.74 (s, 1H), 8.21 (bs, 1H), 7.56 (bs, 1H), 7.17 (d, J = 8.1 Hz, 1H), 6.70-6.61 (m, 2H), 6.56 (d, J = 8.1 Hz, 1H), 3.91 (s, 3H), 3.69 (s, 3H), 2.25-2.10 (m, 1H), 1.65-1.43 (m, 6H), 1.35-1.15 (m, 2H).

(0168)

Example 1 (46)

1-(2-chlorophenyl)-3-methyl-4-(3-methoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0169)

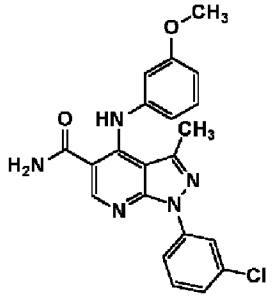
TLC: Rf 0.48 (hexane : ethyl acetate = 1 : 3),

NMR (DMSO-d_6): δ 10.93 (br, 1H), 8.67 (s, 1H), 8.23 (br, 1H), 7.70 (dd, J = 7.7, 1.8 Hz, 1H), 7.66-7.49 (m, 4H), 7.25 (dd, J = 7.7, 7.7 Hz, 1H), 6.78-6.67 (m, 3H), 3.72 (s, 3H), 1.78 (s, 3H).

(0170)

Example 1 (47)

1-(3-chlorophenyl)-3-methyl-4-(3-methoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0171)

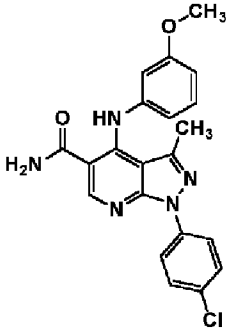
TLC: Rf 0.50 (hexane : ethyl acetate = 1 : 1),

NMR (DMSO-d_6): δ 10.95 (br, 1H), 8.84 (s, 1H), 8.39 (dd, J = 2.0, 2.0 Hz, 1H), 8.28 (br, 1H), 8.22-8.18 (m, 1H), 7.70 (br, 1H), 7.55 (dd, J = 8.1, 8.1 Hz, 1H), 7.38-7.33 (m, 1H), 7.22 (dd, J = 8.0, 8.0 Hz, 1H), 6.79-6.68 (m, 3H), 3.72 (s, 3H), 1.79 (s, 3H).

(0172)

Example 1 (48)

1-(4-chlorophenyl)-3-methyl-4-(3-methoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0173)

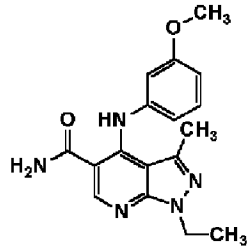
TLC: Rf 0.38 (hexane : ethyl acetate = 1 : 1),

NMR (DMSO-d_6): δ 10.94 (br, 1H), 8.81 (s, 1H), 8.29 (br, 1H), 8.26 (d, J = 9.0 Hz, 2H), 7.69 (br, 1H), 7.58 (d, J = 9.0 Hz, 2H), 7.22 (dd, J = 8.1, 8.1 Hz, 1H), 6.77-6.67 (m, 3H), 3.71 (s, 3H), 1.79 (s, 3H).

(0174)

Example 1 (49)

1-ethyl-3-methyl-4-(3-methoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0175)

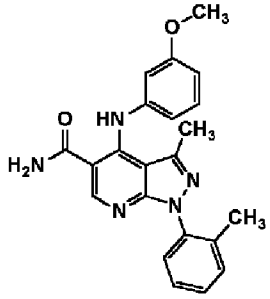
TLC: Rf 0.51 (chloroform : methanol = 9 : 1),

NMR (DMSO-d_6): δ 10.93 (s, 1H), 8.71 (s, 1H), 8.22-8.15 (brs, 1H), 7.60-7.50 (brs, 1H), 7.20 (dd, J = 8.7, 7.8 Hz, 1H), 6.70-6.67 (m, 2H), 6.63 (d, J = 8.7 Hz, 1H), 4.31 (q, J = 7.2 Hz, 2H), 3.70 (s, 3H), 1.69 (s, 3H), 1.35 (t, J = 7.2 Hz, 1H).

(0176)

Example 1 (50)

1-(2-methylphenyl)-3-methyl-4-(3-methoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0177)

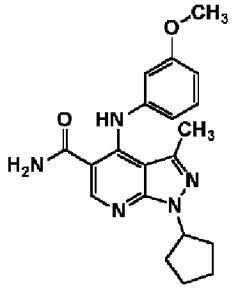
TLC: Rf 0.45 (chloroform : methanol = 9 : 1),

NMR (DMSO-d_6): δ 10.95 (s, 1H), 8.67 (s, 1H), 8.21 (brs, 1H), 7.59 (brs, 1H), 7.45-7.30 (m, 4H), 7.24 (t, J = 8.1 Hz, 1H), 6.80-6.60 (m, 3H), 3.72 (s, 3H), 2.05 (s, 3H), 1.78 (s, 3H).

(0178)

Example 1 (51)

1-cyclopentyl-3-methyl-4-(3-methoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0179)

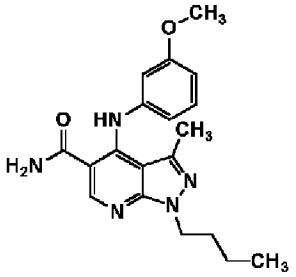
TLC: Rf 0.35 (chloroform : methanol = 10 : 1),

NMR (DMSO-d_6): δ 10.91 (s, 1H), 8.70 (s, 1H), 8.18 (br., s, 1H), 7.54 (br., s, 1H), 7.19 (t, J = 8.4 Hz, 1H), 6.75-6.60 (m, 3H), 5.23 (quintet, J = 7.4 Hz, 1H), 3.70 (s, 3H), 2.10-1.75 (m, 6H), 1.70 (s, 3H), 1.75-1.60 (m, 2H).

(0180)

Example 1 (52)

1-butyl-3-methyl-4-(3-methoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0181)

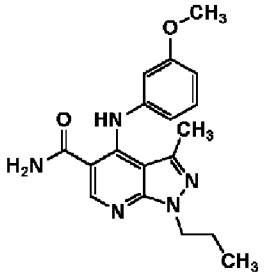
TLC: Rf 0.40 (chloroform : methanol = 9 : 1),

NMR (DMSO-d_6): δ 10.94 (s, 1H), 8.71 (s, 1H), 8.19 (brs, 1H), 7.55 (brs, 1H), 7.23-7.17 (m, 1H), 6.73-6.60 (m, 3H), 4.28 (t, J = 7.0 Hz, 2H), 3.69 (s, 3H), 1.77 (quint, J = 7.0 Hz, 2H), 1.68 (s, 3H), 1.20 (tq, J = 7.0, 7.5 Hz, 2H), 0.87 (t, J = 7.5 Hz, 3H).

(0182)

Example 1 (53)

1-propyl-3-methyl-4-(3-methoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0183)

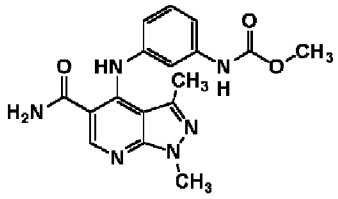
TLC: Rf 0.40 (chloroform : methanol = 9 : 1),

NMR (DMSO-d_6): δ 10.94 (s, 1H), 8.71 (s, 1H), 8.18 (brs, 1H), 7.55 (brs, 1H), 7.23-7.17 (m, 1H), 6.71-6.62 (m, 3H), 4.23 (tq, J = 6.6 Hz, 2H), 3.69 (s, 3H), 1.80 (t, J = 6.6, 7.2 Hz, 2H), 1.69 (a, 3H), 0.81 (t, J = 7.2 Hz, 3H).

(0184)

Example 1 (54)

1-methyl-3-methyl-4-(3-(methoxycarbonylamino) phenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0185)

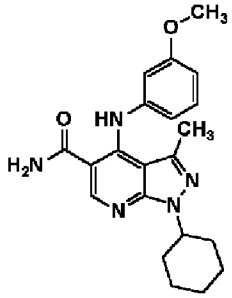
TLC: Rf 0.41 (chloroform : methanol = 10 : 1),

NMR (DMSO-d_6): δ 10.99 (s, 1H), 9.62 (s, 1H), 8.73 (s, 1H), 8.21 (br, 1H), 7.56 (br, 1H), 7.23-7.19 (m, 3H), 6.75-6.71 (m, 1H), 3.87 (s, 3H), 3.61 (s, 3H), 1.67 (s, 3H).

(0186)

Example 1 (55)

1-cyclohexyl-3-methyl-4-(3-methoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0187)

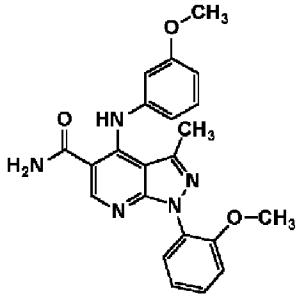
TLC: Rf 0.50 (chloroform : methanol = 9 : 1),

NMR ($CDCl_3$) : δ 10.54 (s, 1H), 8.51 (s, 1H), 7.22-7.15 (m, 1H), 6.73-6.66 (m, 3H), 5.90-5.70 (brs, 2H), 4.78-4.68 (m, 1H), 3.76 (s, 3H), 2.05-1.85 (m, 6H), 1.80 (s, 3H), 1.75-1.20 (m, 4H).

(0188)

Example 1 (56)

1-(2-methoxyphenyl)-3-methyl-4-(3-methoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0189)

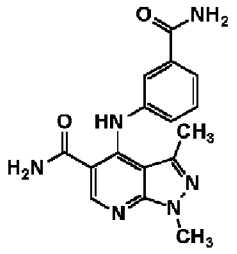
TLC: Rf 0.52 (chloroform : methanol = 9 : 1),

NMR (DMSO-d_6): δ 10.87 (s, 1H), 8.63 (s, 1H), 8.25-8.15 (brs, 1H), 7.62-7.53 (brs, 1H), 7.52-7.46 (m, 1H), 7.38-7.34 (m, 1H), 7.27-7.21 (m, 2H), 7.10-7.05 (m, 1H), 6.74-6.66 (m, 3H), 3.73 (s, 3H), 3.70 (s, 3H), 1.77 (s, 3H).

(0190)

Example 1 (57)

1,3-dimethyl-4-(3-carbamoylphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0191)

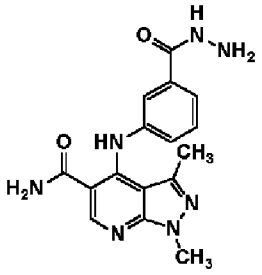
TLC: Rf 0.34 (chloroform : methanol = 10 : 1),

NMR (DMSO-d_6): δ 11.07 (s, 1H), 8.76 (s, 1H), 8.23 (br, 1H), 7.94 (s, 1H), 7.63-7.56 (m, 3H), 7.39 (dd, J = 7.8, 7.8 Hz, 1H), 7.35 (s, 1H), 7.27-7.23 (m, 1H), 3.88 (s, 3H), 1.59 (s, 3H).

(0192)

Example 1 (58)

1,3-dimethyl-4-(3-(aminocarbamoyl) phenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0193)

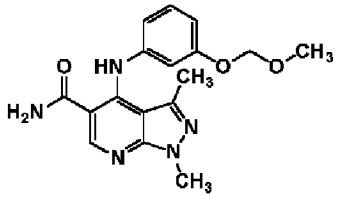
TLC: Rf 0.67 (chloroform : methanol = 5 : 1),

NMR (DMSO-d_6): δ 11.05 (s, 1H), 9.73 (s, 1H), 8.76 (s, 1H), 8.23 (br, 1H), 7.58-7.51 (m, 3H), 7.39 (dd, J = 7.8, 7.8 Hz, 1H), 7.27-7.23 (m, 1H), 4.75-4.35 (m, 2H), 3.88 (s, 3H), 1.58 (s, 3H).

(0194)

Example 1 (59)

1,3-dimethyl-4-(3-(methoxymethoxy) phenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0195)

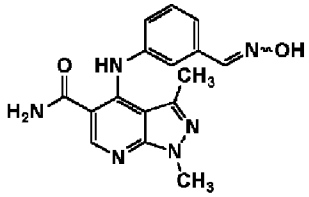
TLC: Rf 0.50 (ethyl acetate),

NMR (DMSO-d_6): δ 10.97 (s, 1H), 8.73 (s, 1H), 8.20 (brs, 1H), 7.55 (brs, 1H), 7.24-7.18 (m, 1H), 6.80-6.68 (m, 3H), 5.12 (s, 2H), 3.88 (s, 3H), 3.31 (s, 3H), 1.69 (s, 3H).

(0196)

Example 1 (60)

1,3-dimethyl-4-(3-((hydroxyimino) methyl) phenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0197)

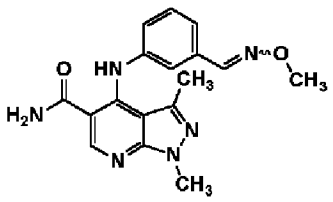
TLC: Rf 0.47 (chloroform : methanol = 8 : 1),

NMR (DMSO-d_6): δ 11.23 (s, 1H), 11.00 (s, 1H), 8.75 (s, 1H), 8.22 (br, 1H), 8.07 (s, 1H), 7.57 (br, 1H), 7.37-7.28 (m, 3H), 7.14-7.09 (m, 1H), 3.88 (s, 3H), 1.66 (s, 3H).

(0198)

Example 1 (61)

1,3-dimethyl-4-(3-((methoxyimino) methyl) phenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0199)

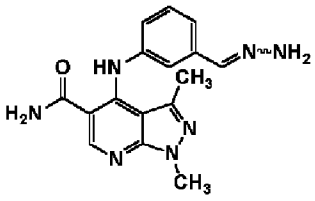
TLC: Rf 0.57 (chloroform : methanol = 8 : 1),

NMR (DMSO-d_6): δ 11.01 (s, 1H), 8.75 (s, 1H), 8.21 (br, 1H), 8.17 (s, 1H), 7.57 (br, 1H), 7.38-7.31 (m, 3H), 7.16-7.11 (m, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 1.65 (s, 3H).

(0200)

Example 1 (62)

1,3-dimethyl-4-(3-((aminoimino) methyl) phenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0201)

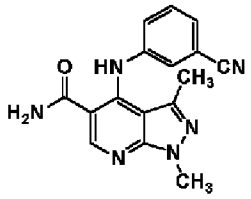
TLC: Rf 0.47 (chloroform : methanol = 8 : 1),

NMR (DMSO-d_6): δ 10.99 (s, 1H), 8.74 (s, 1H), 8.20 (br, 1H), 7.60 (s, 1H), 7.56 (br, 1H), 7.30-7.16 (m, 3H), 6.99-6.96 (m, 1H), 6.77 (s, 2H), 3.88 (s, 3H), 1.64 (s, 3H).

(0202)

Example 1 (63)

1,3-dimethyl-4-(3-cyanophenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0203)

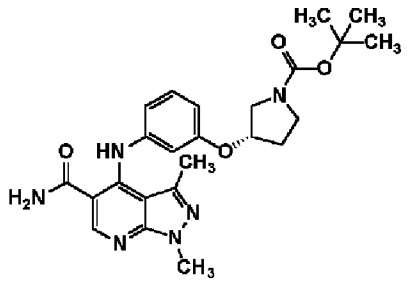
TLC: Rf 0.38 (ethyl acetate),

NMR (DMSO-d_6): δ 10.83 (s, 1H), 8.76 (s, 1H), 8.23 (br, 1H), 7.60 (br, 1H), 7.56-7.44 (m, 3H), 7.41-7.36 (m, 1H), 3.91 (s, 3H), 1.72 (s, 3H).

(0204)

Example 1 (64)

1,3-dimethyl-4-(3-((3S)-1-t-butoxycarbonylpyrrolidin-3-yloxy) phenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0205)

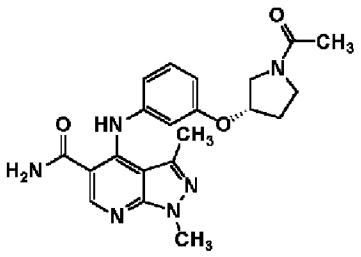
TLC: Rf 0.35 (chloroform : methanol = 9 : 1),

NMR ($CDCl_3$) : δ 10.59 (s, 1H), 8.54 (s, 1H), 7.20-7.15 (m, 1H), 6.78-6.63 (m, 3H), 6.00-5.70 (brs, 2H), 4.85-4.79 (m, 1H), 4.00 (s, 3H), 3.60-3.40 (m, 4H), 2.20-2.00 (m, 2H), 1.78 (s, 3H), 1.46 (s, 9H).

(0206)

Example 1 (65)

1,3-dimethyl-4-(3-((3S)-1-acetyl pyrrolidin-3-yloxy) phenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0207)

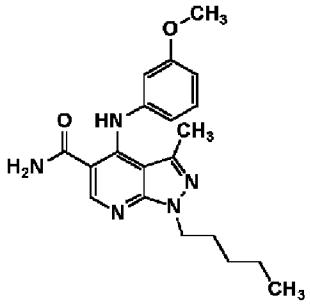
TLC: Rf 0.26 (chloroform : methanol = 9 : 1),

NMR ($CDCl_3$) : δ 10.61, 10.58 (s, 1H), 8.56, 8.55 (s, 1H), 7.23-7.15 (m, 1H), 6.80-6.70 (m, 1H), 6.65-6.61 (m, 2H), 6.00-5.80 (br, 2H), 4.95-4.82 (m, 1H), 4.00 (s, 3H), 3.80-3.50 (m, 4H), 2.32-1.95 (m, 2H), 2.08, 2.04 (s, 3H), 1.79, 1.78 (s, 3H).

(0208)

Example 1 (66)

1-pentyl-3-methyl-4-(3-methoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0209)

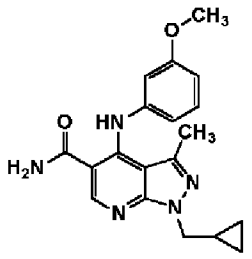
TLC: Rf 0.46 (hexane : ethyl acetate = 2 : 3),

NMR (DMSO-d_6): δ 10.92 (s, 1H), 8.70 (s, 1H), 8.18 (br, 1H), 7.54 (br, 1H), 7.23-7.17 (m, 1H), 6.71-6.67 (m, 2H), 6.65-6.61 (m, 1H), 4.26 (t, J = 7.2 Hz, 2H), 3.69 (s, 3H), 1.84-1.73 (m, 2H), 1.69 (s, 3H), 1.36-1.13 (m, 4H), 0.82 (t, J = 7.1 Hz, 3H).

(0210)

Example 1 (67)

1-cyclopropylmethyl-3-methyl-4-(3-methoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0211)

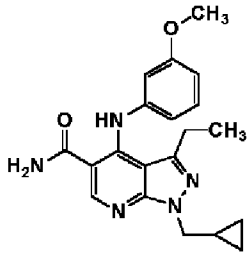
TLC: Rf 0.44 (chloroform : methanol = 10 : 1),

NMR (DMSO-d_6): δ 11.25 (bs, 1H), 8.75 (s, 1H), 8.30 (bs, 1H), 7.64 (bs, 1H), 7.25 (t, J = 7.8 Hz, 1H), 6.84-6.66 (m, 3H), 4.20 (d, J = 7.2 Hz, 2H), 3.72 (s, 3H), 1.68 (s, 3H), 1.35-1.20 (m, 1H), 0.56-0.36 (m, 4H).

(0212)

Example 1 (68)

1-cyclopropylmethyl-3-ethyl-4-(3-methoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0213)

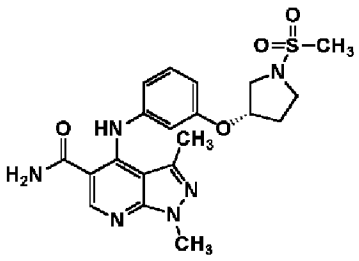
TLC: Rf 0.45 (chloroform : methanol = 10 : 1),

NMR (DMSO-d_6): δ 10.87 (s, 1H), 8.72 (s, 1H), 8.20 (bs, 1H), 7.57 (bs, 1H), 7.19 (t, J = 8.1 Hz, 1H), 6.74-6.56 (m, 3H), 4.19 (d, J = 7.2 Hz, 2H), 3.70 (s, 3H), 2.01 (q, J = 7.5 Hz, 2H), 1.35-1.20 (m, 1H), 0.94 (t, J = 7.5 Hz, 3H), 0.54-0.35 (m, 4H).

(0214)

Example 1 (69)

1,3-dimethyl-4-(3-((3S)-1-mesylpyrrolidin-3-yloxy) phenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0215)

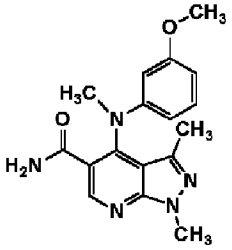
TLC: Rf 0.31 (chloroform : methanol = 9 : 1),

NMR (DMSO-d_6): δ 10.93 (s, 1H), 8.73 (s, 1H), 8.25-8.15 (brs, 1H), 7.60-7.45 (brs, 1H), 7.21 (t, J = 9.0 Hz, 1H), 6.73-6.65 (m, 3H), 5.04-4.99 (m, 1H), 3.87 (s, 3H), 3.52 (dd, J = 11.7, 4.2 Hz, 1H), 3.40-3.25 m, 3H), 2.85 (s, 3H), 2.22-2.00 (m, 2H), 1.68 (s, 3H).

(0216)

Example 2.

1,3-dimethyl-4-(N-methyl-N-[3-methoxyphenyl] amino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0217)

Silver oxide (112 mg) and methyl iodide (568 mg) were added at 0°C under an argon gas stream into a 10 ml anhydrous toluene - 5 ml anhydrous acetonitrile solution of 100 mg of the compound produced in Example 1, and the mixture was stirred at room temperature for 15 hours. The reaction mixture was filtered with celite, and the filtrate was concentrated

under reduced pressure. The residue was refined by silica gel column chromatography (chloroform : methanol = 50 : 1), and 98 mg of a compound of this invention having the following physical property values was obtained.

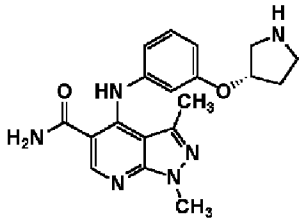
TLC: Rf 0.36 (chloroform : methanol = 9 : 1),

NMR (DMSO-d_6): δ 8.64 (s, 1H), 7.62 (brs, 1H), 7.43 (brs, 1H), 7.03 (t, J = 8.1 Hz, 1H), 6.37-6.33 (m, 1H), 6.17-6.10 (m, 2H), 3.96 (s, 3H), 3.64 (s, 3H), 3.27 (s, 3H), 2.02 (s, 3H).

(0218)

Example 3.

1,3-dimethyl-4-(3-((3S)-pyrrolidin-3-yloxy) phenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide.



(0219)

A 10 % hydrogen chloride solution in methanol (3 ml) was added to a 10 ml ethyl acetate - 10 ml methanol solution of 300 mg of the compound produced in Example 1 (64) and the mixture was stirred at room temperature for 15 hours. The reaction mixture was concentrated under reduced pressure. The residue was adjusted to pH 11 with aqueous saturated sodium carbonate, and thereafter extraction was carried out with ethyl acetate. The extract was washed with aqueous saturated sodium carbonate, dried with anhydrous magnesium sulphate, and thereafter concentrated under reduced pressure, and 125 mg of the compound of this invention having the following physical property values was thereby obtained.

TLC: Rf 0.36 (chloroform : methanol : acetic acid = 10 : 2 : 1),

NMR (DMSO-d_6): δ 10.93 (s, 1H), 8.73 (s, 1H), 8.23-8.12 (brs, 1H), 7.63-7.45 (brs, 1H), 7.21-7.15 (m, 1H), 6.70-6.60 (m, 3H), 4.80-4.75 (m, 1H), 3.87 (s, 3H), 3.31 (brs, 1H), 2.98-2.63 (m, 4H), 1.98-1.82 (m, 1H), 1.70-1.60 (m, 1H), 1.67 (s, 3H).

(0220)

(Preparation Examples)

Preparation Example 1

Each of the following components were mixed in accordance with conventional procedures, and thereafter tabletted, and 100 tablets containing 50 mg of active ingredient per tablet were obtained.

- 1,3-dimethyl-4-(3-methoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide 5.0 g
- carboxymethyl cellulose calcium (disintegrating agent) 0.2 g
- magnesium stearate (lubricating agent) 0.1 g
- microcrystalline cellulose 4.7 g

(0221)

Preparation Example 2

Each of the following components were mixed in accordance with conventional procedures, and thereafter the solution was sterilised in accordance with conventional procedures, packed into ampoules in amounts of 5 ml, freeze-dried in accordance with conventional procedures, and thereby 100 ampoules containing 20 mg of active ingredient per ampoule were obtained.

- 1,3-dimethyl-4-(3-methoxyphenylamino) pyrazolo [5,4-b] pyridin-5-carboxamide 2.0 g
- mannitol 20 g
- distilled water 1000 ml